Is acupuncture as effective as pharmacological management in migraine prophylaxis?

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ABSTRACT

AIM: To assess whether acupuncture is an effective alternative to pharmacological management in the prophylaxis of migraine

RATIONALE: Epidemiological studies suggest that migraine has a huge impact on the world population in terms of pain, side-effects and cost of loss productivity at work.

METHODS: internet based research of relevant and recent randomized controlled trials and subsequent comparative analysis.

RESULTS: Six relevant and recent papers were found to be published on migraine prophylaxis incorporating acupuncture treatment and drug control interventions. All reviewed papers varied considerably in study design and quality, making comparative analysis challenging. Nevertheless, a meta-analysis from the available quantitative data was performed and provided results that are concordant with the cumulative effect of acupuncture treatment. Furthermore, statistically significant increases in the percentage of responders and decreases in rescue medication suggested that acupuncture is an effective prophylaxis for migraine~~s~~ without the adverse events of standard pharmacological management.

CONCLUSION: There is evidence to suggest that acupuncture could be considered as a first line treatment for chronic migraine, particularly in patients who cannot tolerate standardized drug therapy. NICE guidelines may need to be updated. Forthcoming trials need to be redesigned to optimize the full potential of acupuncture in the treatment of migraines.

1. INTRODUCTION

Conditions that have been linked to migraines were described in detail dating back to 3000BC from Babylonian writings. Papyrus scrolls from around 1550BC buried alongside a mummy in Thebes describe very similar symptoms to what we now regard as a migraine.

Hippocrates in 460 BC described a shining light that was typically seen in one eye followed by severe pain that started on one side of the head and enveloped the whole head and down the neck.

Hua T 'o was a Chinese surgeon in the 2nd century who was given credit for the invention of anaesthetic drugs, he was also one of the first to take acupuncture needles to cure migraines. According to Traditional Chinese Medicine: migraines belong to the categories of "Tou Feng" (wind in the head) and "Pian Tou Tong" (pain of the half head) and were either caused by external pathogens or internal excess or deficiency, many of which related to the seven emotions and effecting the Liver.

A headache is a pain of any kind in or around the head. There are several types.

Common visual disturbances during migraine attacks include flashing or coloured lights. Nausea and/or vomiting may occur during an attack. Common prerequisites for a migraine include emotional strain, anxiety or around menstruation. Certain foods, like chocolate, may trigger off migraines and they usually occur between puberty and middle-life.

Attacks differ from person to person, but typically start with visual symptoms. In severe cases, pins and needles may occur or a weakness may arise on one part or sides of the body. These pre-symptoms can last for half an hour, then the pain will start on one side of the head. It will be severe and throbbing. Photophobia may also occur, plus pallor and sweating (Gascoigne, 2001).

Western pharmacological medication may come at a price concerning side effects from long and short term use. Pathologies include nausea, stomach upset, stomach ulcers, irregular or fast heart rate and seizures (Gascoigne, 2001). For the above reasons, this project needs to answer whether acupuncture can be deemed a safe alternative to prophylactic drugs.

Drug treatment for migraines is divided into two broad categories: acute (sudden onset) and prophylactic (to reduce frequency and intensity of recurrent attacks). For the purpose of this

research project only prophylactic will be discussed. It is worth mentioning briefly about the drugs that are used

for prophylactic. Drugs used are divided into six broad categories.

Acupuncture is part of an ancient system of Chinese medicine developed over 2000 years ago. Its core principle is the view of no separation between mind and body and that imbalances in one will generally lead to imbalances in the other (Birch *et al*., 2008). The primary concern of Western medicine is to isolate disease categories or agents of disease where identification of symptoms and causes are the main goal. Chinese medicine, however, considers all physiological and psychological presenting symptoms as well as external environmental factors so forming an overall pattern of disharmony from which a diagnosis and treatment plan can be devised (Kaptchuk *et al.,* 2000).

Acupuncture has gained popularity in the Western hemisphere since the late seventies (Kaptchuk et al., 2000), and as a result of this growth and with the development of evidence-based medicine, there has been increasing demand for acupuncture and Chinese medicine in general to be able to demonstrate its efficacy and effectiveness through the use of rigorous clinical trials in the form of randomised controlled experiments.

Acupuncture is considered a relatively safe therapy with few side effects (BMA 2004), whereas drug therapy has many possible side effects, especially when the patient takes them on a long-term basis.

Successful treatment of headaches and migraines relies on the expertise of the acupuncturist to identify and treat the both Ben and Biao, the affected Zangfu and associated channels.

The primary purpose of this research project was to assess whether acupuncture is an effective alternative to drug therapy as a prophylactic treatment for migraine headaches.

Acupuncture in the West is still not fully accepted, with much doubt, fear and unawareness from the public (MacPherson *et al.*, 2008), because of this, further research is still needed to prove the efficacy and effectiveness of acupuncture as a safe alternative to drug therapy as a prophylactic treatment for migraine headache.

The reason as to why this question needs to be investigated is the fact that epidemiological studies report that migraine headaches have adverse effects on the human population in terms of pain, resources and costs, both personal and to the world national health systems.

2. METHODS

2.1 Identification and selection of studies to be reviewed

A broad search strategy was used in order to identify as many articles as possible. The following databases and sources were searched: PubMed, The Cochrane Central Register of Controlled Trials, The Journal of Chinese Medicine Archive, Allied and Complementary Medicine (AMED), Acubriefs, Acupuncture Research Resource Centre (ARRC).

The search terms used for the electronic databases were: acupuncture, migraine, prophylaxis, prophylactic migraine drugs, flunarizine, metoprolol.

In addition to systematic searches at the beginning of the research project, regular checks were carried out in PubMed in order to identify new studies by searching for migraine and acupuncture. Facco's study was identified in one of these regular checks.

2.2 Criteria for considering studies for this review

Randomized controlled trials were selected for this review, which is to say, controlled trials in which allocation to treatment groups (acupuncture and drug control) was randomized. Study participants had to be diagnosed with suffering from migraine for over one year. The acupuncture treatment involved needle insertion and the control intervention had to be prophylactic drug treatment, excluding acute treatment interventions.

Studies had to be less than 10 years old and had to be original research papers. In addition they had to provide results on outcome measures in which statistical analysis had been performed.

2.3 Data collection and analysis

Abstracts identified during the selection process were read and screened in order to identify candidate studies for inclusion. Full texts of shortlisted papers were obtained and screened in order to carry out the final selection.

Relevant general information was extracted from selected studies using an information extraction form. Information extracted included country, number of recruitment centres, blindness, treatment groups, inclusion of sham acupuncture, number of patients randomized, number of patients treated, number of patients analyzed, number of patients per treatment group, presence of aura, type of acupuncture treatment (standardized, individualized or semi-standardized), duration of acupuncture treatment, number of acupuncture sessions per week,

total number of acupuncture sessions, acupuncturist training and expertise, drug treatment used, drug type, duration of prophylactic drug treatment, type of rescue medication allowed and whether usage was measured, use of headache diaries by patients, duration of baseline period, duration of follow-up period and measurement time points (in weeks and months).

Before quantitative data was extracted, as explained below, outcome measures studied were annotated in the information extraction form, including: proportion of responders, frequency of migraine attacks, migraine days, pain intensity, rescue medication, adverse events, physical and/or mental health questionnaires.

The precise time-points in which studies evaluated their chosen outcome measurements varied considerably. In order to allow for comparative analysis, time-points were grouped as follows: early time-points around 1-2 months after baseline (T1), mid time-points around 3 months after baseline (T2) and around 1 year after baseline (T3).

3. RESULTS

3.1 Comparative description of studies

Six randomised controlled trials that compared the efficacy of acupuncture prophylactic treatment to standard drug controlled interventions were reviewed. They were published between 2002 and 2013.

A total of 1,552 migraine patients participated in the reviewed studies. The mean number of patients in each trial was 259, with a median of 114. The smallest trial included 70 patients and the largest 990. Two trials originated from Germany, two from Italy, one from China and one from Taiwan.

All trials used parallel-group designs. Five trials had two groups (one acupuncture group and a control group) and one trial had three groups (verum acupuncture, sham acupuncture and standard drug treatment). A two-group trial followed a double-dummy design where the acupuncture group was also administered a placebo treatment and the control intervention included sham acupuncture and drug treatment; this design was the only design that allowed patients to be completely blinded to the type of treatment they were receiving. Therefore, two trials (Diener and Wang) used sham acupuncture in their control interventions.

Most trials included patients diagnosed as having migraine with or without aura. One trial (Allais *et al.*, 2002) was restricted to women with migraine without aura.

Acupuncture treatments were semi-standardized in four trials. They included both "basic" points and additional individualized points based on traditional Chinese syndrome diagnosis. Two trials used completely standardized acupuncture treatments.

The length of acupuncture treatment varied to a great extent ranging between 4 weeks and 24 weeks (from 1 month to nearly 6 months) with a median acupuncture treatment of 17 weeks (4 months). The total number of acupuncture sessions was also quite variable among studies, ranging from 10 to 32 sessions, with a median of 16 acupuncture sessions.

The length of control drug treatment also varied widely among studies, ranging from 4 weeks to 24 weeks (1 month to nearly 6 months), with a median of 12 weeks. Two studies compared acupuncture treatment with flunarizine (a calcium-channel blocker), two studies used anti-convulsants (valproic acid and topiramate) as standard prophylactic drug treatment, one study used a beta-blocker drug (metoprolol) and one study used a combination of beta-blockers, flunarizine and valproic acid.

Rescue medication for acute attacks was allowed in all studies. Frequency of rescue medication use was evaluated in all trials as an outcome measurement.

All studies used a headache diary kept by patients for measuring primary outcomes. Trials included a pre-treatment baseline period prior to randomization into the parallel treatment groups. Four out of six trials followed patients for 6 months or more after randomization.

The complex headache data on number of migraine days, frequency, percentage of responders, pain intensity and use of rescue medication were measured and presented in highly variable ways, making systematic extraction and comparison difficult.

Systematic analysis was further complicated by variable follow-up time-points, including 4, 6, 8, 12, 13, 24 and 26 weeks after randomization (Table 4). For comparative purposes time-points were grouped as early (4-8 weeks, 1-2 months), mid (12-13 weeks, 3 months) and late (24-26 weeks, 6 months) time-points.

3.2 Quantitative analysis of outcome measurements

Outcome measurement quantitative data was extracted from the six reviewed studies and represented to allow comparative analysis.

The number of responders was measured in four of the six studies reviewed: Diener, Streng, Wang and Yang. All four studies reported an increase in the

amount of responders (3 months after baseline) in the group treated with acupuncture compared with control interventions. Two studies, Wang and Yang, found these differences to be statistically significant ($p=0.042$ and $p<0.01$, respectively).

Comparative data for the percentage of responders showed that the greatest difference between acupuncture and control groups was found in Yang's study. Yang's included the highest number of total acupuncture sessions (24). This was followed by Wang's, whose study provided 12 acupuncture sessions per patient, and also presented the second highest difference between acupuncture and control groups. Conversely, it was observed that Diener showed the smallest difference in the percentage of responders

between acupuncture and control groups and was also the study with the least total number of acupuncture sessions provided.

A possible correlation between the percentage of responders and the length of treatment was therefore analyzed for this review. Interestingly, the percentage of responders at 3 months showed a very strong correlation ($R^2=0.935$) with the total number of acupuncture sessions received. This data provides evidence that supports the widely held notion that the effects of acupuncture treatment are cumulative and therefore its effects related to the number of acupuncture sessions received. No evidence of correlation was found between the percentage of responders and the length of drug treatment ($R^2=0.001$, data not shown).

Two of the six studies reviewed were designed with a control intervention that included sham acupuncture: Diener (sham control group) and Wang (double-dummy approach). Both studies investigated the percentage of responders and the number of migraine days per month as outcome measurements.

Statistically significant differences in the percentage of responders between acupuncture and control groups were found both in Diener's and Wang's studies. Differences in Diener's study were confined to the first time-point analyzed at around 2 months (T1), with differences not reaching significant values at time-points two and three (T2 and T3). No statistically significant differences between the verum and sham acupuncture groups were reported.

Wang's study showed statistically significant differences in the percentage of responders between the acupuncture and control group (that included sham acupuncture) at both time-points studied (T1 and T2, p=0.043 and p=0.042, respectively).

When the total number of migraine days was investigated, Diener only reported a significant difference between verum and sham groups at the third and last time-point analyzed (6 months). On the other hand, the reduction in the number of migraine days per month was highly statistically significant in Wang's study at both time-points analyzed ($p<0.01$).

Rescue medication for acute migraine attacks was used as an outcome measurement in all six studies reviewed; however, different variables were studied, including: number of analgesic doses taken per month, number of days per month when rescue medication has been used, number of participants taking rescue medication and percentage of participants taking rescue medication.

In order to obtain data that allows inter-study comparisons for this review, data related to the number/percentage of participants taking rescue medication was extracted from three studies (Diener, Wang and Yang) and converted into percentages of participants for comparisons. Two out of the three studies analyzed (Wang and Yang) revealed statistically significant

Linear regression analysis was used to investigate a possible correlation between the percentage of participants taking rescue medication and the total number of acupuncture sessions received. This correlation was found to be moderately strong ($R^2=0.5455$), again providing evidence that supports the cumulative nature of acupuncture treatment.

Five of the six clinical trials reviewed, all but Diener's, provided data in regards to adverse events reported by participants as a result of treatment received. All five studies reported significantly higher numbers of adverse events in participants that were taking prophylactic drugs. These ranged from 10% to 66%, with an average of 44% participants on drugs reporting adverse events compared to an average of 8% of participants receiving acupuncture complaining of adverse events (0-15%).

4. DISCUSSION

A limitation of this project was the fact that only six relevant and recent papers had been published on migraine prophylaxis and therefore available for review. In addition, all six reviewed trials analysed a variety of different outcome measurements, such as pain intensity,

responder rates, migraine days and rescue medication, at differing time points ranging from 4 to 26 weeks and sometimes using different quantitative variables. Furthermore, treatment courses also differed both for acupuncture and drugs in regards to length, number of acupuncture sessions or drug dose.

Their varying designs posed limitations for the systematic analysis and evaluation of their results, making comparisons of the six papers challenging. To improve these limitations, designs of future trials should be more homogeneous, designed in a similar fashion, so as to facilitate future comparative studies that can generate rigorous data to inform clinical practice.

This project provided a comparative study, both quantitatively and qualitatively, of the reviewed papers. A particular strength of this project was its meta-analysis of the available literature in a small scale. This project generated a new data set from the quantitative data extracted from the reviewed papers which allowed the study of the relationship between the number of acupuncture sessions and outcome measurements such as the percentages of responders and the rescue medication use. Results presented in this review showed evidence of strong correlations between the number of total acupuncture sessions administered and the increase in the percentage of responders, and also with the reduction of rescue medication use. Importantly, these results provide new evidence that supports the traditionally held view that acupuncture is cumulative and its effects increase with the number of treatments received.

In the two German trials (Diener et al., 2006) (Streng 2006) a large proportion of patients withdrew informed consent immediately after being allocated to the control (drug) group. Further along these trials additional patients also withdrew. This suggests that some patients that signed for the trial did so with the expectation or hope of being assigned to the acupuncture group, and withdrew if this was not the case. This may be a source of bias.

Interestingly, verum acupuncture did not prove to be superior to sham acupuncture in the reviewed study that used a sham control intervention. This observation is concordant with previous reports (Deng et al., 2007).

There may be three possible explanations: a) acupuncture may act as a potent placebo, b) sham acupuncture may produce direct neuro-physiological changes that may relieve several migraine symptoms and c) due to a lack of blinding, comparisons with routine care and prophylactic drug treatment may be biased (MacPherson *et al.,* 2008).

The average effect of placebo interventions seems to be small (Chan *et al.,* 2004); however, evidence exists that more complex placebos create larger effects (Kaptchuk *et al.,* 2000). Evidence also exists that sham acupuncture has a greater effect than a placebo pill. Available evidence suggest important mechanism for placebo to work include expectations, conditioning, reduction in anxiety and social support (Benedetti, 2008). Acupuncture treatment involves repeated sessions, hands on treatment, empathy, and often, a very personal case history and an individualized diagnosis and treatment plan.

Sham acupuncture protocols involve needling in non-specific TCM points, but with the same frequency and the length as verum acupuncture (Diener et al., 2006) (Wang *et al.,* 2011). Some researchers suggest that most neuro-physiological mechanisms involve in acupuncture do not have to have point specificity (Bäcker *et al.,* 2004). Furthermore, the quality of acupuncture treatment in clinical trials is often disputed. Trials analysed for this review used standardized or semi-standardized needling protocols, which greatly differ from highly individualized routine care. Routine care may also include additional modalities such as Tui Na, cupping and electrotherapy. The challenges lie in designing and conducting clinical trials that suit the complexities of acupuncture treatments, especially when it comes to blinding and selection of control interventions.

Comparative results presented here, particularly in regards to rescue medication and reduction in migraine days, all point towards the fact that acupuncture provides effective prophylaxis for migraines.

Comparisons of prophylactic drugs versus acupuncture find fewer patients reporting adverse effects and a lower dropout rate in favour of all the acupuncture groups reviewed from the six trials. As public awareness increases in regards to the considerable side-effects of prophylactic drugs, acupuncture can only gain popularity over time.

From the National Institute of Clinical Excellence (NICE) guidelines (2012) sections 1.3.16-1.3.18 advise that after taking into consideration the persons preference, comorbidities, risk of adverse effects and the impact on their quality of life from migraines, that topiramate or propanolol can be taken. If neither are suitable of ineffective, a course of 10 sessions of acupuncture should be considered over a period of 5-8 weeks.

This recommendation is a massive leap forward for the credibility of acupuncture treating migraines and for the awareness of acupuncture to the general public. Up to ten sessions are

recommended. Therefore one can expect that acupuncture has a cumulative effect and it would take, by recommendation from NICE, a minimum of ten sessions to show its efficacy and effectiveness over treating migraines.

Several problems arise from this recommendation: a) topiramate and propanolol are still offered as first line treatment and acupuncture as a second recommendation and b) the lack of acupuncture involvement in the infrastructure of the NHS leads to many members of the public unable to afford acupuncture treatment.

In addition, many important issues remain unresolved. The real cost of implementing acupuncture clinics and employing acupuncturists within the infrastructure of the NHS should be evaluated. One successful example in South East London is the Gateway complementary therapy clinic within Lambeth Hospital, which has been running successfully for many years. This model could be replicated in other parts of the country within the infrastructure of the NHS. Optimal treatment length protocols need to be determined by improving study design, thereby allowing migraineurs minimum acupuncture sessions but still providing the maximum migraine-free period, therefore maximising the cost-effectiveness of acupuncture within the National Health System in the UK and potentially all public health systems around the world.

The fact that Europe alone spends 27 billion Euros a year on migraine research (Lekander *et al.*, 2007) and proven research that drugs perform significantly worse than acupuncture when adverse events and side-effects are taken into consideration, should place acupuncture in the forefront of migraine prophylaxis.

5. CONCLUSION

Evidence presented in this review suggests that acupuncture is an effective treatment for chronic migraineurs, particularly in patients who cannot tolerate the vast array of implicated side-effects associated with standardized drug therapy.

NICE guidelines may need to be updated to incorporate acupuncture as a first line treatment on a par with the current pharmacological drugs such as topiramate and propanolol.

Designs of future trials should aim to be more homogeneous so as to facilitate future comparative studies that can generate rigorous data to inform clinical practice. In addition, future study design should aim to optimize the full potential of acupuncture in the treatment

of migraines; they should aim at more closely replicating the individualized treatment provided in routine care environment, which also incorporates additional TCM modalities.

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