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Acupuncture for autistic spectrum disorder (Protocol)

Cheuk DKL, Wong V, Chen WX

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[Intervention Protocol]

Acupuncture for autistic spectrum disorder

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objectives of this systematic review are to determine the effectiveness and safety of acupuncture therapy in patients with autism spectrum disorder. We intend to assess whether acupuncture:

1. is effective in reducing social, communication and behavioural impairments;

2. can improve the quality of life and overall functioning;

3. is associated with any adverse effects.

BACKGROUND

Description of the condition

Autistic spectrum disorder (ASD) is a developmental disorder of children characterized by the triad of impairments of social interaction, social communication, and social imagination (Wing 1997). Repetitive and stereotyped behaviour are often associated with ASD (Wing 1997). The term includes autistic disorder, Asperger syndrome and pervasive developmental disorder (not otherwise specified). The impairments of ASD have a severe impact on learning and social functioning which may persist into adulthood. Autistic spectrum disorder has an estimated prevalence from 5 to 63 children per 10,000 , and there is an increasing trend as higher prevalence rates have been reported from recent studies (Chakrabarti 2001, Fombonne 1999). More recently, an overall figure of 116 in 10,000 has been reported (Baird 2006). This is of great concern to the practicing pediatrician because of an astonishing 556% reported increase in pediatric prevalence between 1991 and 1997, to a prevalence higher than that of spina bifida, cancer, or Down syndrome (Muhle 2004). No prevalence studies have ever been performed on adults.

Autism is a behavior syndrome with multiple aetiologies. There are a few specific genetic conditions that can be associated with ASD (Folstein 1991). Among of cases unknown etiology, there is ample evidence for a higher genetic liability to autism in siblings of probands (those under genetic investigation) than expected from the population prevalence (Folstein 1991).The identity and number of genes involved remain unknown (Muhle 2004). The wide phenotypic variability of the ASDs likely reflects the interaction of multiple genes within an individual's genome and the existence of distinct genes and gene combinations among those affected (Muhle 2004). Epidemiologic studies indicate that environmental factors such as toxic exposures, teratogens, perinatal insults, and prenatal infections such as rubella and cytomegalovirus account for few cases (Muhle 2004). Immunolgical bases for neurological injure leading to ASD has been proposed (Krause 2002). It is suggested that ASD might result from an interaction between genetic, environmental, and immunological factors, with oxidative stress as a mechanism linking these risk factors (Chauhan 2006). Recently, research has focused on the role of synapse structure and function as central to the development of autism and suggests possible targets of interventions (Rapin 2008).

Autistic spectrum disorder is heterogeneous with many associated problems, such as associations with particular genetic disorders [fragile X, single gene disorders (tuberosis sclerosis, untreated phenylketonuria, and possibly neurofibrotosis)] (Folstein 1991), epilepsy (the medical condition most highly associated with autism) (Muhle 2004) and various comorbid psychiatric disorders including mood disorders (major depressive disorder, bipolar disorder), anxiety disorders (specific phobic disorder, separation anxiety disorder, social phobia, generalized anxiety disorder, obsessive compulsive disorder) and disruptive disorders (attention-deficit hyperactivity disorder, oppositional defiant disorder) (Leyfer 2006), which render it difficult to be sure about effectiveness of therapies. The problems and manifestations of autism spectrum disorder might change with time along with other developmental abnormalities. It is also likely that outcomes of treatment will depend on timing of therapy in relation to age and onset or progression of problems.

Description of the intervention

Various behavioral interventions for ASD are widely used without rigorously documented evidence (Bryson 2003, Barlow 2004). Pharmacological treatments have been, at best, useful adjuncts to behavioural intervention with improvements in problems such as attention deficit, sleep disturbance, mood disorder, self-harm or aggression to others (Posey 2001, Gringras 2000). Many aspects of ASD are still debatable with elusive and complex etiology and no agreement on effective therapy exists. Frustrated parents are therefore eager to explore different forms of complementary and alternative medicine (CAM) (AAP 2001, Levy 2003; Harrington 2006; Wong 2006; Hanson 2007).

The estimated prevalence of CAM in children with ASD outnumbers that in the general population, ranging from 31.7% in Philadelphia (Levy 2003), to as high as 95% in New York and New Jersey (Harrington 2006). A recent study (Wong 2009) surveyed a cohort of Hong Kong Chinese with ASD and/or other neurodevelopmental disabilities. Of these, about 40% of ASD children reported previous use of CAM, with acupuncture being the most common form.

Acupuncture is a procedure in which specific body areas, the meridian points, are pierced with fine needles for therapeutic purposes. It is one of the major modalities of treatment in Traditional Chinese Medicine. Its use can be traced back more than 2000 years in China (Wu 1996). Reported to be a relatively simple, inexpensive and safe treatment, acupuncture has been well accepted by Chinese patients and is widely used in various neurological and other disorders as an alternative treatment approach (Johansson 1993). Acupuncture is also increasingly practiced in some Western countries (NIH 1998).

However, it is worrying that many CAM therapies including acupuncture that claim to be effective in ASD have not actually undergone stringent scientific testing. Therefore, as one of most common forms of CAM, an evidence-based systematic review regarding acupuncture for ASD needs to be undertaken.

How the intervention might work

Wellness has been used in the context of alternative medicine since 1950s (Dunn 1961), which is extensively adopted to mean a healthy balance of the mind, body and spirit. Wellness pro-

grams offer alternative medicine techniques to improve wellness, although whether these techniques actually improve health remains controversial and debatable.

Acupuncture involves complex theories of regulation of five elements (fire, earth, metal, water, and wood), Yin and Yang, Qi, blood and body fluids. By stimulating various meridian points, disharmony and dysregulation of organ systems is corrected to relieve symptoms and restore natural internal homeostasis (Maciocia 1989).

There is no strong evidence to show the correspondence of meridians or acupoints to any anatomical feature. The main view believes a close proximity exists between acupoints and the nervous system (Fu 2000). One study (Dung 1984) investigated the anatomical features of acupoints and found that structures in the vicinity of acupoints exclusively involved nerves; therefore, it is hypothesized that by inserting fine needles into these nerve-innervated acupoints, a sequence of neurological responses would be elicited. These reposes can occur locally or close to the site of application (Jansen 1989), or at a distance, mediated mainly by sensory neurons to many structures within the central nervous system (Magnusson 1994). This can lead to activation of pathways affecting various physiological systems in the brain as well as in the periphery (Sun 2001; Middlekauff 2004; Liu 2004). The effect of acupuncture had been demonstrated in animal and human studies to be due to direct neural stimulation, changes in neurotransmitters such as endorphin, immunological markers or endocrinological signals (Stux 1998).

Like many CAM forms of treatment, the Traditional Chinese Medicine (TCM) approach to treating ASD is holistic. The pathogenesis of ASD according to TCM is 'derangement and insufficiency of brain and mind' (Chen 2008). The pathologic involvement is in the brain, relating to the heart, pericardium, liver, spleen and kidney (Chen 2008). In traditional Chinese acupuncture, nearly 400 acupoints on the body surface are interrelated to various functions linked through 14 meridians to various organs or viscera of the human body. By stimulating various meridian points, acupuncture may be able to correct the disharmony and dysregulation of organ systems, which might be involved in various dimensions of ASD, to relieve symptoms and restore the mind and body. The scientific basis of how acupuncture could ameliorate different cognitive and behavioral dimensions of autism has not been well studied and the mechanisms of how acupuncture works is likely to be very complex, given the vast number of acupoints involved in the treatment of this complicated disease.

Why it is important to do this review

Acupuncture is claimed to be effective in treating virtually all diseases; however, it remains uncertain whether the existing evidence supports the use of acupuncture for patients with autistic spectrum disorder.

OBJECTIVES

The objectives of this systematic review are to determine the effectiveness and safety of acupuncture therapy in patients with autism spectrum disorder. We intend to assess whether acupuncture:

1. is effective in reducing social, communication and behavioural impairments;

2. can improve the quality of life and overall functioning;

3. is associated with any adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled clinical trials using truly random or quasi-random allocation of treatment will be included in the review. Quasi-randomisation may involve, for example, alternate allocation or allocation by birthdate.
2. Studies comparing acupuncture with at least one control group that uses no treatment, placebo treatment or sham treatment will be included.
3. Parallel group and crossover designs will be included.

Types of participants

People of any age and both genders with autism spectrum disorders such as autistic disorder or pervasive developmental disorder diagnosed by standard criteria such as the DSM or ICD criteria. Diagnosis by assessment tools such as Autism Diagnostic Observation Scale (ADOS) (Lord 1997), Autism Diagnostic Interview-Revised (ADI-R) (Lord 1994), the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing 1999) and the 3di (Skuse 2004) are also accepted.

Types of interventions

Trials evaluating all forms of acupuncture therapy including acupressure, laser acupuncture or electroacupuncture will be included in the review regardless of number of times of treatment and length of treatment period. Either traditional acupuncture in classical meridian points or contemporary acupuncture in non-meridian or trigger points will be included regardless of the source or methods of stimulation (e.g. hand, needle, laser, or electrical stimulation). The control interventions will be no treatment, placebo acupuncture or sham acupuncture. Placebo acupuncture refers to a needle attached to the skin surface (not penetrating the skin but at the same acupoints) (Furlan 2005). Sham acupuncture refers to a

needle placed in an area close to but not in acupuncture points (Furlan 2005) or subliminal skin electrostimulation via electrodes attached to the skin (SCSSS 1999).
Comparisons that will be investigated are listed below:
1. acupuncture only compared to no treatment;
2. acupuncture only compared with placebo or sham treatment;
3. acupuncture in addition to baseline medication or treatment compared with baseline medication or treatment alone;
4. acupuncture in addition to baseline medication or treatment compared with placebo or sham treatment in addition to baseline medication or treatment.

Trials that compared only different forms of acupuncture or comparing acupuncture with other forms of treatment will be excluded.

Types of outcome measures

Primary outcomes

Behavioural observations and standardised assessments of autistic behaviours

Secondary outcomes

1.Communication and linguistic ability by standardised measurements
2. Cognitive functioning by standardised measurements
3. Global functioning measurements
4. Quality of life measurements
5. Adverse effects
As ASD is a spectrum disorder, different parents may have different concerns for their children. However, the dominant aim of different interventions for ASD is to improve the global functions via ameliorating various sub-aspects such as behavior, language, and cognitive function, with the ultimate aim of improving the quality of life.
Behavioral problems in patients with ASD are myriad and variable. Many behavioral dimensions are usually assessed together in standardised instruments. Different instruments may subcategorise behavioural disturbances in different ways; therefore behavioral problems are not further subcategorised in the protocol, but some examples of potentially relevant instruments are listed below.
Examples of behavioral assessment tools adopted for evaluation of ASD include the Aberrant Behavioral Checklist (ABC) (Aman 1986) , Ritvo-Freeman Real Life Scale (RFRLS) (Freeman 1986) and the Autism Treatment Evaluation Checklist (ATEC) (Rimland ND). In addition, the Parental Stress Index (PSI) (Abidin 1995) can be used as a measure for parental concern of behavioural disturbances.
Instruments for evaluating communication and linguistic abilities may include the Reynell Language Developmental scale (RLDS) (Edwards 1997), the Symbolic Play Test (SPT), (Lowe 1976), and the Arabic language test for language (Allam 2008).
Instruments for evaluating general cognitive functioning include the Griffiths Mental Developmental Scale (GMDS) (Griffiths 1996) and the Leiter International Performance Scale-Revised (Leiter-R) (Leiter 1980).
Instruments for evaluating global functioning might include the Pediatric Evaluation Disability Inventory (PEDI) (Haley 1992) or the Functional Independence Measure for Children, or 'WeeFIM' (Msall 1994).
Instruments for evaluating quality of life may include for example the WHOQOL-BREF (WHO 1993), which has been used in some ASD studies (Shu 2009, Mugno 2007).
The most common adverse events of acupuncture are needle pain, tiredness, and bleeding (Ernst 2001). Feeling of faintness and syncope were uncommon and pneumothorax is rare (Ernst 2001). Patients with ASD may experience adverse effects of acupuncture but may be unable to convey relevant information to their parents or the researchers due to impairment of communication. Generally, the side effects of acupuncture should be monitored in the studies. The prevalence of various adverse effects will be reported and analysed in the current systematic review if sufficient data are identified.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue), MEDLINE, EMBASE, PsycINFO, Dissertation Abstracts International, CINAHL, AMED (the Allied and Complementary Medicine Database), and TCMLARS (Traditional Chinese Medical Literature Analysis and Retrieval System) which is a database of Chinese biomedical research literature. We will also search relevant clinical trials and research databases including the National Center for Complementary and Alternative Medicine, the National Institute of Health Clinical Trials Database, the Chinese Acupuncture Trials Register and the Trials Register of the Cochrane Complementary Medicine Field. The China Journals Full-text Database, China Master Theses Full-text Database, China Doctor Dissertations Full-text Database, China Proceeding of Conference Database, and Index to Chinese periodical literature on WWW (tw) will also be searched.
The following search strategy, using a combination of controlled vocabulary and text word terms, will be used for MEDLINE, and will be modified to suit other databases:
To search for autism spectrum disorder, we will use the following strategy:
1. exp CHILD-DEVELOPMENT-DISORDERS-PERVASIVE/
2. COMMUNICATION/
3. AUTIS$.tw

4. PDD .tw
5. PERVASIVE DEVELOPMENTAL DISORDER$.tw
6. LANGUAGE adj/3 DELAY
7. COMMUNICAT$
8. SPEECH adj/3 DISORDER$
9. CHILDHOOD SCHIZOPHRENIA
10. KANNER$
11. ASPERG$
12. or/1-11

To search for acupuncture, we use the following strategy:

1. exp acupuncture therapy/
2. acupunc$.tw
3. acupress$.tw
4. electroacupunc$.tw
5. meridian$.tw
6. acupoint$.tw
7. or/1-6

Finally, we will combine the results of the above two strategies with the highly sensitive search strategy for randomised controlled trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

The Chinese translation of autism is equivalent to "Self Shut-Off Syndrome" in Hong Kong and Taiwan while in Mainland China, it is known as the "Lonely Syndrome".

The following Chinese key words (either simplified or complex characters) were also used for retrieving relevant Chinese database: "ZiBiZheng"(Self Shut-off Syndrome), GuDuZheng (lonely Syndrome), "ZhenJiu" (Acupuncture). "ZhenCi" (Acupuncture), "DianZhen" (Electro-acupuncture), "ZhenYa" (Acupressure), "ErZhen" (Ear Acupuncture), "TiZhen" (Body acupuncture), "SheZhen" (Tongue acupuncture), "TouPiZhen" (Scalp acupuncture) and "XueWei" (acupoint).

Searching other resources

The reference lists of all relevant papers will be searched for further studies.

The process of searching many different sources may bring to light direct or indirect references to unpublished studies. We will seek to obtain copies of such unpublished material. In addition, we will contact colleagues and experts in the field to ascertain any unpublished or ongoing studies.

There is no language restriction in the search and inclusion of studies.

Data collection and analysis

Selection of studies

Two review authors will independently review titles and abstracts of references retrieved from the searches and will select all potentially relevant studies. Copies of these articles will be obtained, and reviewed independently by the same reviewers against the inclusion criteria of the study. Reviewers will not be blinded to the names of the authors, institutions or journal of publication. The review authors will then extract data from included trials and assess trial quality independently. All disagreements will be resolved by consensus.

Data extraction and management

The following data will be extracted:

(1) Study methods
a. Design (e.g. parallel or crossover design).
b. Randomisation method (including list generation)
c. Method of allocation concealment
d. Blinding method
e. Stratification factors
(2) Participants
a. Inclusion/exclusion criteria
b. Number (total/per group)
c. Age and sex distribution
d. Specific diagnosis/diagnostic subtypes
e. Co-morbidities
f. Duration of disorder
g. Previous treatments
(3) Intervention and control
a. Type of acupuncture
b. Details of treatment regime including duration of treatment
c. Type of control
d. Details of control treatment including drug dosage
e. Details of co-interventions
f. Washout period in cross-over design
(4) Follow-up data
a. Duration of follow-up
b. Dates of treatment withdrawal and reasons for treatment withdrawal
c. Withdrawal rates
(5) Outcome data as described above
(6) Analysis data
a. Methods of analysis (intention-to-treat/per-protocol analysis)
b. Comparability of groups at baseline (yes/no)
c. Statistical techniques

Data will be entered on to RevMan 5.0 by one reviewer (Chen WX) and then checked by the second reviewer (Cheuk DKL).

Assessment of risk of bias in included studies

Risk of bias will be assessed independently by two review authors according to the Cochrane Collaboration Handbook (Higgins 2008). Review authors will independently assess the risk of bias within each included study based on the following six domains with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias):

Sequence generation

Description: the method used to generate the allocation sequence will be described in detail so as to assess whether it should have produced comparable groups; review authors' judgment: was the allocation concealment sequence adequately generated?
Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Allocation concealment

Description: the method used to conceal allocation sequence will be described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment; review authors' judgment: was allocation adequately concealed?

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Blinding

Description: any measures used to blind participants, personnel and outcome assessors will be described so as to assess knowledge of any group as to which intervention a given participant might have received; review authors' judgment: was knowledge of the allocated intervention adequately prevented during the study?
Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Incomplete outcome data

Description: If studies do not report intention-to-treat analyses, attempts will be made to obtain missing data by contacting the study authors. Data on attrition and exclusions will be extracted and reported as well the numbers involved (compared with total randomized), reasons for attrition/exclusion where reported or obtained from investigators, and any re-inclusions in analyses performed by review authors; review authors' judgment: were incomplete data dealt with adequately by the reviewers? (See also 'Handling missing data', below).

Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Selective outcome reporting

Description: attempts will be made to assess the possibility of selective outcome reporting by investigators by contacting authors for any non-reported findings; review authors' judgment: are reports of the study free of suggestion of selective outcome reporting?
Ratings: 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias)

Other sources of bias

We will assess if the study was apparently free of other problems that could put it at a high risk of bias.

Measures of treatment effect

Binary outcomes

Relative risk with 95% confidence intervals (CI) will be used for binary outcomes.

Continuous outcomes

Weighted mean difference with 95% CI will be used for continuous outcomes. If studies use the same rating scales, weighted mean differences (WMD) and 95% confidence intervals will be calculated. If studies use different scales to measure the same outcomes, the standardized mean difference (SMD) will be calculated with 95% confidence intervals.
All analyses will include all participants in the treatment groups to which they were allocated if data are available.

Unit of analysis issues

There may be unit of analysis issues when cross-over trials are included in the meta-analysis. The cross-over trials will be assessed to see whether: (i) the cross-over design is suitable; (ii) there is a carry-over effect; (iii) only first period data are available; (iv) correct analysis has been performed; and (v) comparability of results with those from parallel-group trials. Where appropriate, the results of the cross-over trials will be combined with results of parallel-group trials.
When conducting a meta-analysis combining the results of cross-over trials, we will use the inverse variance methods recommended by Elbourne (Elbourne 2002). Where data presented from a cross-over trial is restricted (and more information is not available from the original investigators) we will use the presented data within the first phase only, up to the point of cross-over.

Dealing with missing data

Handling missing data: In the first instance, authors will be contacted to supply data missing from included studies. Missing data and drop-outs/attrition will be assessed for each included study, and the extent to which the results/conclusions of the review could be altered by the missing data will be assessed and discussed. If less than 70% of patients allocated to the treatments are not reported on at the end of the trial, for a particular outcome, those data will not be used as they will be considered to be too prone to bias. Differential drop-outs in the intervention group will also be noted and reasons assessed as these can potentially bias the study results.

Assessment of heterogeneity

Investigation of heterogeneity: Clinical heterogeneity will be assessed by comparing the distribution of important participant factors between trials (age, gender, specific diagnosis/diagnostic subtypes, duration of disorder, associated neuropsychiatric diseases), and trial factors (randomisation concealment, blinding, losses to follow-up, treatment type, co-interventions). Statistical heterogeneity will be assessed by examining (Higgins 2002), a quantity which describes approximately the proportion of variation in point estimates that is due to heterogeneity rather that sampling error. In addition, chi-squared test of homogeneity will be employed to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

Assessment of bias: Funnel plots (effect size against standard error) will be drawn if sufficient studies are found. Asymmetry could be due to publication bias, but can also be due to a relationship between trial size and effect size. In the event that a relationship is found, clinical diversity of the studies will be examined (Egger 1997).

Data synthesis

Where the interventions are the same or similar enough, we plan to synthesize results in a meta-analysis if there is no important clinical heterogeneity. Both the fixed-effect model and the random-effect model will be used in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

Sub-group analysis: Analysis of a number of sub-groups can lead to misleading conclusions (Higgins 2008), and are best kept to a minimum. If data permit, we will conduct sub-group analyses for different age groups, diagnostic subtypes or severity of disease.

Sensitivity analysis

Sensitivity analyses will be conducted to assess the impact of studies with different levels of risk of bias
in particular, those using adequate methods of allocation concealment such as sealed opaque envelopes or telephone randomisation versus those using methods which are inadequate or unclear.

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* *Indicates the major publication for the study*

WHAT'S NEW

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CONTRIBUTIONS OF AUTHORS

DKL Cheuk: conceiving the review, designing the review; coordinating the review; data collection for the review; designing search strategies; undertaking searches; screening search results; organizing retrieval of papers; screening retrieved papers against eligibility criteria; appraising quality of papers; extracting data from papers; writing to authors of papers for additional information; obtaining and screening data on unpublished studies; data management for the review; entering data into RevMan; analysis of data; interpretation of data; providing a methodological perspective; providing a clinical perspective; writing the protocol.

WX Chen: data collection for the review; designing search strategies; undertaking searches; screening search results; organizing retrieval of papers; screening retrieved papers against eligibility criteria; appraising quality of papers; extracting data from papers; writing to authors of papers for additional information; obtaining and screening data on unpublished studies; data management for the review; entering data into RevMan; analysis of data; interpretation of data; providing a methodological perspective; providing a clinical perspective; writing the protocol.

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DECLARATIONS OF INTEREST

No potential conflict of interest is known.