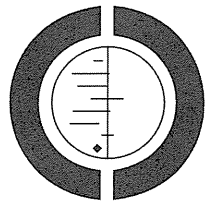
Hypnosis for induction of labour (Protocol)

Nishi D, Shirakawa MN, Ota E, Hanada N, Mori R



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[Intervention Protocol]

Hypnosis for induction of labour

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ABSTRACT

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

The primary objective of the study is to investigate whether hypnosis is an effective means of inducing labour.

BACKGROUND

Description of the condition

Labour induction is a method to artificially stimulate uterine contractions in order to bring about childbirth. This method is a common obstetric intervention carried out to address a variety of complications, such as prolonged pregnancy, maternal illness or fetal death. In recent years the rate of labour induction has been rapidly increasing (Grobman 2007) and approximately 10% of 300,000 deliveries across 24 countries were induced, ranging from 1.4% in Niger to 35.5% in Sri Lanka (WHO 2011). Possible complications that lead to induction of labour include post-term pregnancy, prelabour rupture of membranes, hypertensive disorders (e.g. gestational hypertension, pre-eclampsia, or eclampsia), maternal medical complications (e.g. diabetes mellitus, abruptio placentae), fetal death, fetal growth restriction, suspected fetal macrosomia (large baby), chorioamnionitis (inflammation of the fetal membranes), multiple pregnancy, vaginal bleeding and other complications (ACOG 2009; WHO 2011). A related Cochrane review shows that a policy of labour induction compared with expectant management in postterm women is associated with fewer perinatal deaths and fewer caesarean sections (Gulmezoglu 2012). However, induced labour can also give rise to increased complications, such as bleeding, caesarean section, uterine hyperstimulation and rupture (WHO 2011). Although not advocated in current guidelines, induction of labour is sometimes elected by pregnant women, or for the convenience of clinicians (WHO 2011).

There are a variety of methods available for induction, including the following: pharmacological methods (e.g. administration of oxytocin, prostaglandins, hyaluronidase, corticosteroids, or oestrogen); mechanical methods (e.g. manually rupturing the amniotic membranes, membrane sweeping, laminaria tents or balloon catheters); and alternative medicine methods (e.g. acupuncture, hypnosis or non-invasive interventions). It can be complicated to balance the benefits and risks of each method. For instance, a recent systematic review suggested that prostaglandin E2 (PGE2) reduced the possibility of failure to deliver vaginally within 24 hours and vaginal misoprostol reduced the need for caesarean deliveries, but both interventions heightened the risk of uterine hyperstimulation (Mozurkewich 2011). Mechanical methods such as laminaria tents and balloon catheters reduced uterine hyperstimulation, but increased maternal and neonatal infectious complications (Mozurkewich 2011). Given these possible problems, complementary and alternative medicine (CAM) methods may provide a safer strategy. Hypnosis comes under this category. Up to now, it has been used mostly during active labour while its effectiveness in the induction of labour is largely unknown. The purpose of this protocol is to search out evidence of its use and benefits, if any, in induction.

Description of the intervention

Hypnosis is a technique that enhances concentration and increases suggestibility, while simultaneously decreasing sensory awareness (Barrows 2003).

According to the Society for Psychological Hypnosis, Division 30 of the American Psychological Association, a definition of hypnosis is as follows: "Hypnosis typically involves an introduction to the procedure during which the subject is told that suggestions for imaginative experiences will be presented. The hypnotic induction is an extended initial suggestion for using one's imagination, and may contain further elaborations of the introduction. A hypnotic procedure is used to encourage and evaluate responses to suggestions. When using hypnosis, one person (the subject) is guided by another (the hypnotist) to respond to suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought or behavior. Persons can also learn self-hypnosis, which is the act of administering hypnotic procedures on one's own. If the subject responds to hypnotic suggestions, it is generally inferred that hypnosis has been induced" (Green 2005).

Hypnosis is practiced as hypnotherapy in psychotherapy and has applications in many other fields, including pain management (Montgomery 2000). The effect of hypnosis is thought to be mediated by the brain's anterior cingulate cortex (ACC) (Raymond 2005), which is understood to be involved in processing negative emotional responses (Etkin 2011). A growing body of literature suggests that the ACC in the brain is critically involved in the processing of anxiety (Allman 2001; Shin 2010), meaning that hypnosis could play a role in minimising an anxious emotional response from this part of the brain. The method can be administered either by a hypnotherapist or through self-hypnosis, which women can learn to master during their pregnancy.

How the intervention might work

It is currently unknown how hypnosis works for induction of labour. However, a case report suggests that hypnosis might effect better relaxation of the cervix (Eat 1960). Also, hypnosis may enhance self-esteem (Tarem 1992; Valente 1990), self-confidence, mastery and well-being (Simkin 2004), which can help to reduce anxiety in pregnant women. Maternal conditions of anxiety were significantly associated with the onset of labour in a comparative analysis of induced and spontaneous labours in the UK (Humphrey 2009). Recently, oxytocin has been considered to have anxiolytic or anxiety-relieving effects (Meinlschmidt 2008; Neumann 2011), and a previous study showed a significant negative correlation between oxytocin and anxiety (Scantamburlo 2007). Thus it might be plausible to hypothesise that women who are extremely anxious about their impending labour are unable to produce the oxytocin necessary to stimulate contractions, and therefore, may find the relaxing properties of hypnosis beneficial. These findings hold promise for the application of hypnosis as a potentially effective technique to induce labour by decreasing stress in pregnant women.

Why it is important to do this review

Although there have been various reviews of CAM methods to manage pain during labour and childbirth (Cyna 2004; Jones 2012; Madden 2012), randomised controlled trials on hypnosis related to labour induction have not been fully evaluated. There have been some case reports or series on the effects of hypnosis on labour induction (Cyna 2003; Fee 1966; Race 1961), but a lack of formal evidence. As induced labour is a standard obstetric intervention experienced by pregnant women when complications arise during pregnancy, it is important to find methods of labour induction that have minimal significant side effects. Hypnotic techniques have been used in obstetrics for over a 100 years (Werner 1982). A meta-analysis conducted by Cyna 2004 showed significantly less use of labour augmentation by oxytocin and an increased incidence of women delivering spontaneously in the hypnosis usage group. Reducing pharmaceutical interventions will prevent associated side effects. Few previous studies reported the costs of providing hypnosis in labour (Jones 2012). However, Cyna suggested that it was expected to be low in relation to the total costs of an episode of care, so it may be associated with substantial decreased costs to the healthcare system if effective (Cyna 2006). This review will set out a clear summary of the effectiveness of hypnosis for induction of labour and its potential significance to healthcare professionals and consumers who are seeking safe, alternative methods of labour induction.

OBJECTIVES

The primary objective of the study is to investigate whether hypnosis is an effective means of inducing labour.

METHODS

Criteria for considering studies for this review

Types of studies

All published and unpublished randomised controlled trials (RCTs) of acceptable quality comparing hypnosis with no intervention or any other interventions, where the primary outcome is to assess whether there is labour induction. We will include RCTs in which the unit of randomisation is individuals and clusters. We will exclude quasi-RCTs or cross-over trials.

Types of participants

Pregnant women.

Types of interventions

We will include studies comparing pregnant women receiving hypnosis as a method of labour induction with those receiving no intervention or any other interventions for labour induction.

Types of outcome measures

Primary outcomes

1. Vaginal delivery within 96 hours or within the duration defined by the trialist
2. Caesarean section

Secondary outcomes

Maternal outcomes

1. Serious maternal morbidity or death (e.g., uterine rupture, admission to intensive care unit, septicaemia)
2. Uterine hyperstimulation
3. Epidural analgesia
4. Instrumental vaginal delivery
5. Postpartum haemorrhage defined by the trial authors
6. Maternal satisfaction
7. Caregiver satisfaction
8. Chorioamnionitis

Neonatal outcomes

1. Serious neonatal morbidity or perinatal death (e.g., seizures, birth asphyxia defined by the trial authors, neonatal encephalopathy, disability in childhood)
2. Neonatal admission to special care and/or intensive care unit
3. Apgar score at five minutes less than seven

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register.
This register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Identified through the searching activities described above are each assigned to a review topic. The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

a) Handsearching: we will handsearch relevant journals and other sources including cross-references.
b) Personal communication: we will contact key personnel and organisations in the relevant field for published and unpublished references.
c) We will search conference proceedings of national and international conferences related to hypnosis interventions and will list these in the review.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

Two review authors (D Nishi, MN Shirakawa) will independently assess for inclusion all potential studies identified as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third author (E Ota).

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third author. We will enter data into Review Manager software (RevMan 2012) and check it for accuracy.
When information regarding any of the above is unclear e.g. abstracts only, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (DN, MNS) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement through discussion or by involving a third assessor (EO).

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.
We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.
We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.
We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias.
We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as a summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multi-armed trials

We will include multi-armed trials in the analyses. We will combine all relevant methods of hypnosis into a single group and incorporate all relevant control groups into a single group. Any other different intervention will be addressed in different meta-analyses. If one of the arms is irrelevant, we will exclude it from the analysis.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.
For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as substantial if an I^2 is greater than 30% and either a T^2 is greater than zero, or there is a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry

is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We will carry out statistical analysis using the Review Manager software (RevMan 2012). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials' populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials.
If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.
We plan to carry out the following subgroup analyses:

1. previous caesarean section versus no previous caesarean section;
2. nulliparity versus multiparity;
3. membranes intact versus ruptured;
4. cervix favourable versus unfavourable or undefined;
5. history of previous induction of labour versus no history of induction;
6. preterm (36 weeks or less) delivery versus term delivery (37 weeks to 41 weeks) versus postterm delivery (42 weeks or more).

Only the primary outcome will be included in the subgroup analyses. We will assess subgroup differences using interaction tests available within RevMan (RevMan 2012). We will report the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We will perform a sensitivity analysis if the review might affect the results due to the high risk of bias of some of the included trials. For the purpose of this sensitivity analysis, we will define 'high quality' as a trial having low risk of random sequence generation, adequate allocation concealment and the percentage of missing data less than 20%, given the stated importance of attrition as a quality measure (Tierney 2005). Only the primary outcome will be included in the sensitivity analyses. If statistical heterogeneity exists in outcomes, we will carry out the sensitivity analysis to explore the effects of fixed- or random-effects analyses. Furthermore, if there are any assumptions for ICC value used in cluster-randomised trials, we will perform a sensitivity analysis.

ACKNOWLEDGEMENTS

We thank Ms Emma Barber for her editorial support.

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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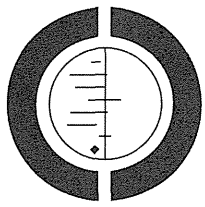
Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period (Review)

Yaju Y, Kataoka Y, Eto H, Horiuchi S, Mori R



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[Intervention Review]

Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period

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ABSTRACT

Background

There are several Cochrane systematic reviews looking at postpartum haemorrhage (PPH) prophylaxis in the third stage of labour and another Cochrane review investigating the timing of prophylactic uterotonics in the third stage of labour (i.e. before or after delivery of the placenta). There are, however, no Cochrane reviews looking at the use of interventions given purely after delivery of the placenta. Ergometrine or methylergometrine are used for the prevention of PPH in the postpartum period (the period after delivery of the infant) after delivery of the placenta in some countries. There are, furthermore, no Cochrane reviews that have so far considered herbal therapies or homeopathic remedies for the prevention of PPH after delivery of the placenta.

Objectives

To assess the effectiveness of available prophylactic interventions for PPH including prophylactic use of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, administered after delivery of the placenta, compared with no uterotonic agents as well as with different routes of administration for prevention of PPH after delivery of the placenta.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (30 April 2013), The Food and Drug Administration (FDA) (USA), Medicines and Healthcare Products Regulatory Agency (MHRA) (UK), European Medicines Agency (EMA) (EU), Pharmaceuticals and Medical Devices Agency (PMDA) (Japan), Therapeutic Goods Administration (TGA) (Australia), ClinicalTrials.gov, Current Controlled Trials, WHO International Clinical Trials Registry Platform (ICTRP), University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: Japan), Japan Pharmaceutical Information Center Clinical Trials Information (Japic-CTI: Japan), Japan Medical Association Clinical Trial Registration (JMACCT CTR: Japan) (all on 30 April 2013) and reference lists of retrieved studies

Selection criteria

All randomised or quasi-randomised controlled trials comparing prophylactic ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies (using any route and timing of administration) during the postpartum period after delivery of the placenta with no uterotonic agents or trials comparing different routes or timing of administration of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, during the postpartum period after delivery of the placenta.

Data collection and analysis

Two review authors independently assessed trial eligibility and the methodological quality of trials, extracted data using the agreed form. Data were checked for accuracy.

Main results

Five randomised studies involving 1466 women met the inclusion criteria. All studies were classified as having an unclear risk of bias. Two studies (involving 1097 women) compared oral methylergometrine with a placebo, and one (involving 171 women) compared oral methylergometrine with Kyuki-choukeisu-in, a Japanese traditional herbal medicine. The remaining two studies (involving 198 women) did not report the outcomes of interest for this review. None of the included studies reported primary outcomes prespecified in the review protocol (blood loss of 1000 mL or more over the period of observation, maternal death or severe morbidity). Overall, there was no clear evidence of differences between groups in the following PPH outcomes: blood loss of 500 mL or more (risk ratio (RR) 1.45; 95% confidence interval (CI) 0.39 to 5.47, two studies), amount of lochia during the first 72 hours of the puerperium (mean difference (MD) -25.00 g; 95% CI -69.79 to 19.79, one study), or amount of lochia by four weeks postpartum (MD -7.00 g; 95% CI -23.99 to 9.99).

The Japanese study with a relatively small sample size comparing oral methylergometrine with a Japanese traditional herbal medicine found that oral methylergometrine significantly increased the blood haemoglobin concentration at day one postpartum (MD 0.50 g/dL; 95% CI 0.11 to 0.89) compared to herbal medicine. Adverse events were not well-reported in the included studies. We did not find any studies comparing homeopathic remedies with either a placebo or no treatment.

Authors' conclusions

There was insufficient evidence to support the use of prophylactic oral methylergometrine given after delivery of the placenta for the prevention of PPH. Additionally, the effectiveness of prophylactic use of herbal medicine or homeopathic remedies for PPH is still unclear as we could not find any clear evidence. Trials to assess the effectiveness of herbal medicines and homeopathic remedies in preventing PPH are warranted.

PLAIN LANGUAGE SUMMARY

Prophylactic interventions after delivery of placenta for reducing bleeding during the postnatal period

Haemorrhage following childbirth (postpartum haemorrhage) is a major cause of maternal death and health problems in resource-poor settings in both low- and high-income countries. Postpartum haemorrhage is defined as blood loss from the genital tract of more than 500 mL, generally occurring within the first 24 hours after delivering the placenta and occasionally between 24 hours and six to 12 weeks. Possible causes are the uterus (womb) failing to contract after delivery (uterine atony), a retained placenta, inverted or ruptured uterus, and cervical, vaginal, or perineal lacerations. To address these issues, the joint policy statements between the International Confederation of Midwives, the International Federation of Gynecology and Obstetrics, and the World Health Organization recommend 'active management of third stage of labour', which includes the administration of a uterotonic drug (intravenous oxytocin), just before or just after delivery in order to help the uterine muscles to contract. The use of oral uterotonic drugs such as methylergometrine for the prevention of postpartum haemorrhage after delivery of the placenta is not recommended in the joint policy statements. Yet orally delivered uterotonic drugs, such as ergot alkaloids (including methylergometrine), herbal therapies, or homeopathic remedies are easy-to-administer agents that may be considered as possible alternatives after delivery of the placenta in developing countries, as in Japan. We set out to determine whether such agents are effective in preventing haemorrhage after childbirth. We found a total of five randomised clinical trials (involving 1466 women). In three of the trials (involving 1268 women), oral methylergometrine was compared with placebo (two trials) or the Japanese traditional herbal medicine Kyuki-choukeisu-in (one trial). The other two trials (involving 198 women) did not report information on relevant outcomes of interest for this review. Overall, there was no clear evidence that prophylactic oral methylergometrine was effective in reducing haemorrhage after childbirth. The trials were not of good quality

and adverse events were not well-reported. We did not find any completed trials looking at the effectiveness of homeopathic remedies in reducing haemorrhage after childbirth. The effectiveness of such remedies warrants further investigation.

BACKGROUND

Description of the condition

Postpartum haemorrhage (PPH), or excessive bleeding at or after childbirth is a leading cause of maternal mortality and morbidity worldwide, accounting for approximately a quarter of deaths that occur as a consequence of complicated pregnancy (WHO 2005). Although the majority of these deaths occur in developing countries, industrialised countries also suffer from direct cause-related maternal mortality such as PPH. Several recent publications have documented an increasing incidence in PPH over time in resource-affluent settings (Cameron 2006; Ford 2007; Joseph 2007), including Australia, Canada, the UK, and the USA (Knight 2009). The postpartum period is generally deemed to start after delivery of the infant. PPH is generally defined as blood loss from the genital tract in excess of 500 mL with severe postpartum haemorrhage (SPPH) being a loss of 1000 mL or more, and very SPPH being a loss of 2500 mL or more. PPH in the third stage of labour and PPH within the first 24 hours following delivery of the placenta (so called immediate PPH or primary PPH) form the majority of postpartum complications (Cunningham 2010). PPH or SPPH, however, occasionally develop even in the postpartum period between 24 hours and six to 12 weeks (so called delayed/late PPH or secondary PPH) (ACOG 2006). Therefore, the postpartum period between 24 hours and six to 12 weeks can also be a potentially hazardous period during childbirth. The dominant cause of primary PPH is uterine atony, whereas, secondary PPH can be associated with various causes. Secondary PPH is caused due to subinvolution of the placental site, retained products of conception, infection and inherited coagulation defects (ACOG 2006). Clinically problematic uterine haemorrhage develops within one to two weeks in 1% of women. Such bleeding predominantly occurs due to the abnormal involution of the placental site (Cunningham 2010).

Common causes of primary or secondary PPH include failure of the uterus to contract adequately after birth (atonic PPH), genital tract trauma (traumatic PPH), bleeding due to retention of placental tissue and coagulation disorders. Atonic PPH is the most prevalent among all of these conditions. In an effort to prevent uterine atony and associated bleeding, administering oxytocin soon after delivery is a routine management therapy (ACOG 2006). The joint policy statements between the International Confederation of Midwives (ICM) and the International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO) have recommended active management of the third stage of labour that includes the administration of oxytocin or another uterotonic drug within one minute after the birth of the child, early umbilical cord clamping and cutting, controlled cord traction, and uterine massage after delivery of the placenta, as deemed appropriate. However, use of uterotonic drugs for the prevention of PPH after delivery of the placenta was not recommended in the statements (ICM-FIGO 2003; ICM-FIGO 2006; WHO 2009).

The use and management of drug therapies to prevent PPH after delivery of the placenta remains unclear. However, some studies (Andersen 1998; De Groot 1996a; Van Setia 1995) have reported different types of ergot alkaloids, and varying routes and timing of administration of prophylactic measures. Oral ergometrine or methylergometrine were considered as possible alternative prophylactic oxytocics that were easy to administer and suitable for use in developing countries (De Groot 1996b). Likewise, in a resource-affluent country such as Japan, the use of these prophylactic medications following delivery of the placenta is routinely administered (Okada 2005).

According to the published reviews investigating the role of oral ergometrine or methylergometrine, these medications are not satisfactory alternatives to parenteral prophylactic oxytocic drugs for the prevention of PPH for at least three reasons: using the tablets orally, they are less effective, unstable, and pharmacokinetically unreliable (De Groot 1996b; De Groot 1998). Therefore, effectiveness and safety of the prophylactic use of ergometrine following delivery of the placenta needs to be backed up by clear evidence.

Moreover, a varying number of agents are administered either in herbal forms or as homeopathic remedies for the third stage of labour management (Brucker 2001). Therefore, it can be assumed that apart from ergot alkaloids, numerous prophylactic interventions (e.g. herbal therapies, homeopathic remedies, and other oxytocic drugs) do exist to help with the prevention of PPH after delivery of the placenta. However, the effectiveness and safety of these prophylactic interventions are yet to be investigated.

Description of the intervention

Intramuscular or intravenous ergometrine and methylergometrine are, in general, used in the management of the third stage of labour

and for the prevention of puerperal haemorrhage (WHO 2009). Oral ergometrine or methylergometrine were considered to be possible alternative oxytocics that were easy to administer and suitable for use in developing countries (De Groot 1996b). In Japan, methylergometrine is administered orally for the prevention of secondary PPH in women in the postnatal period after delivery of the placenta (Okada 2005).

Furthermore, herbal medicines or homeopathic remedies in the forms of tablets, tea or other preparations can also be used during the third stage of labour (Brucker 2001).

How the intervention might work

There are three groups of uterotonic agents: ergot alkaloids, oxytocin, and prostaglandins. The mechanisms through which these uterotonic agents work for the prevention of PPH are however, different. Oxytocin and prostaglandin function through oxytocin/prostaglandin receptors in the myometrium leading to fast and long-lasting rhythmic contractions. Ergometrine and methylergometrine are the most common types of ergot alkaloids and increase the muscle tone of the uterus with continuous (not rhythmic) tetanic contractions resulting in compressed myometrial blood vessels (De Groot 1998).

Ergometrine and methylergometrine improve uterine involution contributing to secondary PPH prevention, in which uterine subinvolution of the placental site is likely to be the underlying cause (ACOG 2006; Cunningham 2010). However, administration of ergometrine and methylergometrine may increase the risk of hazardous side effects in mothers such as hypertension and other complications of vasoconstriction. Moreover, intoxicated cases with severe complications including apnoea, coma, and convulsions in newborns have also been documented (Acke 2003).

Prescribing herbal or homeopathic medicines on the other hand, depends on the characteristics of individual patients. Therefore, the overall concept of administering herbal or homeopathic medicines for PPH prevention is different to conservative Western medication therapies. Yet, herbal or homeopathic medicines must be considered as drug therapies, and therefore, evaluating the effectiveness of the usage of these non-conventional agents is equally important.

Why it is important to do this review

PPH continues to be a challenge in the prevention of maternal morbidity and mortality. Establishing useful methods for preventing PPH that are effective and safe are of vital importance. Administration of ergometrine or methylergometrine in the postpartum period might be one such useful method. Several Cochrane reviews investigating PPH prophylaxis in the third stage of labour (i.e., before or after the delivery of the placenta) looked at both of these drugs (Begley 2011; Cotter 2010; Lidsmerakel 2011; McDonald 2009; Mori 2012; Novikova 2011; Oladapo 2012; Rohwer 2012; Su 2012; Tungalp 2012) as well as other measures (Hofmeyr 2010; Peña-Martí 2010; Soltani 2011). Another Cochrane review examined the timing of prophylactic uterotonics in the third stage of labour (Soltani 2010). Current evidence provided from these Cochrane reviews, in general, favours active management over passive management of this stage of labour, involving administration of a prophylactic oxytocic before delivery of the placenta. However, there are no Cochrane reviews looking at the use of prophylactic interventions given purely after delivery of the placenta. In addition, there are no Cochrane reviews investigating herbal therapies or homeopathic remedies for the prevention of PPH after delivery of the placenta.

Existing evidence indicates that ergometrine or methylergometrine are used for the prevention of PPH in the postpartum period after delivery of the placenta in developing countries, including a high-income country, Japan. However, the effectiveness and safety of prophylactic usage of these drugs are not clear and must therefore be systematically assessed. Furthermore, understanding the balance between the risks and benefits of such an intervention is crucial.

OBJECTIVES

To assess the effectiveness of available prophylactic interventions for PPH including prophylactic use of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies, administered after delivery of the placenta, compared with no uterotonic agents as well as with different routes of administration for prevention of PPH after delivery of the placenta.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised or quasi-randomised (such as alternate allocation or allocation by health insurance number, hospital record, etc.) controlled trials comparing prophylactic ergometrine, methylergometrine, or other agents (using any route and timing of administration) with no uterotonic agents during the postpartum period after delivery of the placenta, or comparing different routes or timing of administration of ergotamine, ergometrine, methylergometrine, herbal therapies, and homeopathic remedies during the postpartum period after delivery of the placenta. We included well-conceptualised studies that provided sufficient information for the targeted evaluation. Studies that did not provide sufficient

information for the targeted evaluation were incorporated into the 'Studies awaiting classification' category until they are published as full reports.

Types of participants

Women who have had a spontaneous vaginal delivery.

Types of interventions

Ergometrine, methylergometrine, or other agents administered by any route or timing of administration for the prevention of postpartum haemorrhage after delivery of the placenta.

Comparisons

1. Ergometrine/methylergometrine versus placebo/no treatment.
2. Ergometrine/methylergometrine administration via different routes: oral versus intravenous, oral versus intramuscular or subcutaneous, intravenous versus intramuscular or subcutaneous.
3. Herbal medicine versus ergometrine/methylergometrine (any route or dosage), or versus placebo/no treatment.
4. *Homeopathic remedy versus one of the following:* ergometrine/methylergometrine (any route or dosage), herbal medicine, placebo/no treatment.
5. Other agents versus ergometrine/methylergometrine (any route or dosage), or versus placebo/no treatment.

Types of outcome measures

Primary outcomes

- Blood loss of 1000 mL or more over the period of observation (as determined by the trial investigator)
- Maternal death or severe morbidity (e.g., major surgery, organ failure, hyperpyrexia, intensive care unit admission, hysterectomy, compression sutures, artery ligations, or as defined by trial authors)

Secondary outcomes

- Maternal death; individual components of severe morbidity (as listed above or as defined by the trial authors)
- Blood loss of 500 mL or more over the period of observation (as determined by the trial investigator)
- Blood transfusion
- Use of therapeutic uterotonics
- Additional treatment for postpartum haemorrhage (uterine tamponade, X-ray, embolisation)
- Side effects reported either individually or combined, when appropriate, e.g., vomiting, nausea, elevation of diastolic blood pressure, shivering, headache, chest pain, shortness of breath, pyrexia, and diarrhoea
- Postnatal anaemia (defined by trial authors, absolute or relative drop in haemoglobin)
- Thromboembolic events
- Cost involved in the treatment sought
- Amount of lochia (vaginal discharge after giving birth) during the first 72 hours postpartum (outcome not prespecified)
- Amount of lochia by four weeks postpartum (outcome not prespecified)
- Duration of lochia of more than four weeks (outcome not prespecified)
- Endometritis (outcome not prespecified)
- Pain requiring analgesia (outcome not prespecified)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (30 April 2013).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

To find clinical trials for approval of new drugs, we also searched the following databases through 30 April 2013:

- The Food and Drug Administration (FDA) in the USA
- The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK
- The European Medicines Agency (EMA) in the EU

- The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan
- The Therapeutic Goods Administration (TGA) in Australia

For ongoing trials, we searched the following trial registers through 30 April 2013:

- ClinicalTrials.gov
- Current Controlled Trials
- The WHO International Clinical Trials Registry Platform (ICTRP)
- University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; Japan)
- Japan Pharmaceutical Information Center Clinical Trials Information (Japic-CTI; Japan)
- Japan Medical Association Clinical Trial Registration (JMACCT CTR; Japan)

Searching other resources

We checked references cited in papers identified through the above search strategy to retrieve additional relevant studies.

We also considered abstracts for inclusion, if sufficient information was provided.

We did not apply any language restrictions.

Data collection and analysis

Selection of studies

The inclusion of studies identified through the search strategy was independently assessed by two review authors, Yukari Yaju (YY) and Yuko Kataoka (YK). We resolved any disagreement through discussion among the review authors.

Data extraction and management

We designed a form that would enable us to extract data. For eligible studies, two review authors (YY, YK) used the form to extract the data independently. We resolved discrepancies through discussion among the review authors. We used the Review Manager software (RevMan 2011) for data entry and checked the accuracy of the data entry. When information about the studies was unclear, we contacted the authors of the original reports to obtain further details. We contacted the authors of two studies (Andersen 1998; Arabin 1986) to request details on random sequence generation and prespecified outcomes and received a satisfactory answer from the author of one study (Arabin 1986). We contacted the author of one study (Ishihara 2003) to ask about inconsistency in blood haemoglobin concentrations reported in his article and he provided an appropriate answer. Further, we contacted the author of one study (Grunberger 1983) to request details of outcomes but received no reply. The review authors were not blinded to the names of authors, journals, or institutions.

Assessment of risk of bias in included studies

Two review authors (YY, YK) independently assessed risk of bias in each included study using The Cochrane Collaboration's tool for assessing risk of bias, outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and contained in RevMan (RevMan 2011). Any disagreement was resolved by discussion.

(1) Sequence generation (checking for possible selection bias)

For each included study, we described the method used in the sequence generation process in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the methods as:

- yes (low risk of bias) (any truly random process, e.g. referring to a random number table, using a computer random number generator, minimisation method);
- no (high risk of bias) (any non-random process, e.g. odd or even date of birth, some rule based on date or day of admission, some rule based on hospital or clinic record number); or
- unclear (uncertain risk of bias) (insufficient information about the sequence generation process to permit judgement of 'yes' or 'no').

(2) Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

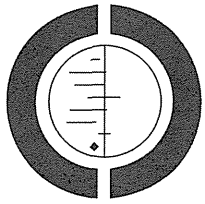
We assessed the methods as:

- yes (low risk of bias) (e.g. central allocation including telephone, web-based and pharmacy-controlled randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes);
- no (high risk of bias) (using an open random allocation schedule such as a list of random numbers, assignment envelopes without appropriate safeguards [e.g., unsealed or non-opaque], alternation or rotation, date of birth, case record number, any other explicitly unconcealed procedure); or
- unclear (uncertain risk of bias) (insufficient information to *permit judgement of 'yes' or 'no'*).

(3) Blinding of participants, personnel and outcome assessors (checking for possible performance bias)

Vitamin K supplementation during pregnancy for improving outcomes (Protocol)

Shahrook S, Hanada N, Sawada K, Ota E, Mori R



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[Intervention Protocol]

Vitamin K supplementation during pregnancy for improving outcomes

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ABSTRACT

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

To assess the effects of vitamin K supplementation administered to pregnant women for improving maternal and neonatal outcomes.

BACKGROUND

Description of the condition

Vitamin K deficiency can present a serious health risk to pregnant women and their babies that may lead to haemorrhage, especially in newborns. Haemorrhaging occurs due to reduced levels of prothrombin - an important element of the blood dependent on vitamin K for coagulation - that slows down the blood-clotting process and may result in excessive maternal or neonatal bleeding (Shils 2006). Vitamin K deficiency is extremely rare among the general adult population, although it may occur when vitamin absorption is impaired due to an underlying pathology (Food and Nutrition Board 2001; WHO/FAO 2004). It is largely unknown what type of crucial role vitamin K plays during pregnancy (UMMC 2011). However, as nutritional requirements generally increase in pregnancy, the risks of clinically relevant deficiencies also escalate, especially among pregnant women with poor nutritional status (Greenlick 2009).

Ingestion of certain therapeutic drugs such as carbamazepine and heparin anticonvulsants may also impede vitamin K metabolism in pregnant women and give rise to vitamin K deficiency (Davidson 1986; Shils 2006). Women's exposure to vitamin K anticoagulants during pregnancy may affect the fetus in utero, resulting in coumarin embryopathy (CE) (Hetzel 2006). Approximately 6% of newborns exposed to maternal coumarin intake during pregnancy develop CE, with skeletal anomalies (e.g. midfacial hypoplasia and epiphyseal calcifications) found in 80% of these babies. Central nervous malformations (e.g. midline structural defects) were detected in 45% of babies diagnosed with CE; and signs of intracranial haemorrhage were observed in 10% (Van Driel 2002). Moreover, since coumarins cross into the placenta, they later affect fetal coagulation which increases the risk of intracranial haemorrhage before birth (Van Driel 2002). Women's consumption of therapeutic drugs during pregnancy may be associated with maxillonasal hypoplasia in newborns in the first trimester, which can lead to problems with facial and orthodontic development (Howe 1994). Van Driel 2002 and colleagues observed that of the pregnant women who were administered with coumarins, a vitamin K anticoagulant or blood-thinning medicine, 22% experienced miscarriage (Van Driel 2002). However, there is insufficient evidence to support a link between vitamin K deficiency and miscarriage.

Women of reproductive age undergoing bariatric surgeries for obesity-related morbidity treatment may also experience adverse pregnancy outcomes associated with various nutritional deficiencies (ACOG 2015). Women are likely to experience frequent nutritional shortages following bariatric surgery, but the risks of severe deficiencies are greater after malabsorption-inducing surgery rather than procedures that are solely restrictive (Guelinckx 2009). Deficiencies of vitamin K, vitamin B_{12}, and some trace minerals have previously been reported in pregnant women who have undergone bariatric surgery (Guelinckx 2009; Shankar 2010).

Vitamin K deficiency bleeding (VKDB) is a bleeding disorder in young infants with inadequate levels of vitamin K that can lead to haemorrhaging inside the infant's skull soon after birth (Shearer 2009). Infants are born with naturally low levels of vitamin K and do not receive adequate amounts from breast milk due to the slower transfer rate through the placenta (Shearer 2009). Premature infants with vitamin K shortages and impaired oral absorption are more susceptible to vitamin K deficiency immediately following birth (Shearer 1992). The onset of early VKDB, for example, occurs among infants from birth or 24 hours immediately prior to delivery (Lane 1985). Maternal drug consumption affecting vitamin K metabolism may typically increase this condition among infants (McNinch 1985; Stevenson 1985). Therefore, coagulation disorders require immediate treatment with vitamin K administration prior to diagnosis. In Western European countries, the incidence of late VKDB in infants without vitamin K prophylaxis was found to be 5/105 births versus 11 and 72/105 births in Japan and Thailand, respectively (Shearer 2009). Immediately following birth, the proportion of VKDB infants who received no vitamin K administration was estimated to be 0.01% to 0.44% (Kazmi 2010). A mortality rate of 20% was also estimated in newborns with severe bleeding disorders, including intracranial haemorrhage (50%), and common persistent neurologic impairment (McNinch 1981; Van Kries 1992).

Several adverse pregnancy outcomes affect babies born to women with epilepsy (WWE). Evidence suggests that anticonvulsant drugs may impede folic acid and phytomenadione (vitamin K) metabolism causing higher risks of neural tube defects and early haemorrhage among newborns (Nulman 1999). It has been recommended that pregnant women who take phenobarbital, carbamazepine or phenytoin should commence maternal phytomenadione supplementation four weeks prior to the delivery due date (Nulman 1999). Although uncommon, the use of vitamin K antagonists during pregnancy can give rise to liver disease in neonates (Hetzel 2006). Hetzel 2006 suggests that vitamin K antagonists should be highly controlled during anti-coagulation in pregnant women with mechanical heart valves.

Description of the intervention

Pregnant women deficient in vitamin K may need to incorporate vitamin K supplements into their prenatal vitamin regimen. In certain disease conditions such as cystic fibrosis, coeliac disease, or Crohn's disease in which sufficient vitamin K absorption is impaired, vitamin K supplementations are essential, especially in the form of a multivitamin that contains vitamin K, which is regarded as more beneficial than vitamin K supplementation alone (UMMC 2011). Pregnant women taking anticonvulsant drugs are recommended to take vitamin K two weeks prior to delivery (UMMC 2011). Vitamin K status in pregnant women who take prothrombin-depressing anticoagulants, such as coumarin, should be carefully assessed (Institute of Medicine 1998). Women without these conditions who experience a normal pregnancy are generally not required to take vitamin K supplements unless, for example, they are diagnosed with malabsorption syndrome or are taking antibiotics such as cephalosporins, which inhibit vitamin K absorption by destroying vitamin K-forming bacteria as well as bacteria that is harmful to the body (UMMC 2011).

Vitamin K formulation and prophylactic administration differ by country (WHO/FAO 2004). For example, in the United States, vitamin K1 or phylloquinone is available as a supplement either separately or as a component of a multivitamin complex in 5 mg tablets (UMMC 2011). Vitamin K is widely sold over the counter as water-soluble chlorophyll tablets, capsules, or liquid (UMMC 2011). Vitamin K is administered parenterally or orally, and various reported doses have been administered to pregnant women: for example, 10 mg of intravenous or intramuscular vitamin K daily for two to seven days (Liu 2006); one 10 mg dose of vitamin K intramuscularly, repeated again after four days followed by 20 mg daily of oral vitamin K (Kazzi 1988); 10 mg of intramuscular vitamin K between four and 96 hours before delivery (Padiak 1998); and 10 mg of vitamin K1 daily is recommended for pregnant women on anticonvulsant therapy from 36 weeks of pregnancy onwards (Cornelissen 1993).

There is insufficient evidence to show that excessive vitamin K ingestion has toxic effects on the human body. As vitamin K passes through the placenta and is found in breast milk, pregnant and lactating women should seek advice from their health practitioner before commencing vitamin K supplements (UMMC 2011). However, oxidative damage, red cell fragility, and methaemoglobin may develop in cases of high doses of water-soluble vitamin K3 (menadione) consumption, and local hypersensitivity reactions, mostly due to vitamin K1 dermal injections, may also occur (Expert Group on Vitamins and Minerals 2003). A daily intake of 1 mg or less is unlikely to have any harmful effects according to guidelines from the United Kingdom (NHS 2011). Also, as toxicity for the oral consumption of vitamin K remains unknown, 10 to 20 mg or more of phylloquinone is recommended to be safe for common clinical administration in the United States (WHO/FAO 2004). Furthermore, patients with chronic fat malabsorption who take such doses have shown no evidence of side

effects (WHO/FAO 2004). Synthetic menadione and its derivatives are not recommended, particularly for vitamin supplements in newborns (WHO/FAO 2004). Moreover, due to interactions with certain drugs and the potential for side effects, vitamin K supplements are restricted for pregnant and lactating women, as vitamin K passes through the placenta and is found in breast milk; warfarin consumers; and those with a rare metabolic disease called glucose-6-phosphate dehydrogenase (G6PD) deficiency (UMMC 2011).

How the intervention might work

Antenatal administration of vitamin K supplementation for pregnant women may provide significant benefits for improving both maternal and neonatal outcomes. Vitamin K supplementation may improve the deficiency of factor VII in megaloblastic anaemia of pregnancy with thrombocytopenia (Morris 1965). Adequate supplementation that includes vitamin K and other essential micronutrients has been recommended for pregnant women who have undergone bariatric surgery in order to remedy maternal and fetal complications such as severe anaemia, congenital abnormalities and low birthweight (Gudzinzka 2009; Shanker 2010). Furthermore, maternal administration of vitamin K has been suggested to improve prothrombin and partial thromboplastin activities and reduce the incidence and severity of intraventricular haemorrhage (IVH) in infants (Morales 1988; Pomerance 1987) although a Cochrane review (Crowther 2010) shows no impact of vitamin K in preventing IVH. Antenatal vitamin K supplementation may help to reduce the risk of haemorrhagic complications in infants born to WWE who take antiepileptic drugs during pregnancy (Choulika 2004; Kaaja 2002), including a reduction in the occurrence of vitamin K deficiency in such infants (Cornelissen 1993).

Why it is important to do this review

The effects of vitamin K deficiency, especially haemorrhagic complications, other adverse outcomes and the need for vitamin K supplementation, have mostly been reported in relation to neonates. Vitamin K deficiency, remedial supplementation and associated morbidities in women of reproductive age, specifically during pregnancy, have not been well described. Evaluation of the efficacy and safety of different treatment regimens for vitamin K supplementation during pregnancy is therefore crucial to improve maternal and neonatal outcomes. A previous Cochrane review examined the effect of vitamin K supplementation, including women at risk of imminent very preterm birth in the prevention of neonatal periventricular haemorrhage (PVH) and associated adverse outcomes in preterm neonates (Crowther 2010). Therefore, in this protocol and subsequent review, we will include all pregnant women regardless of their pregnancy stage and we will aim to assess the effects of vitamin K supplementation on a set of neonatal and maternal outcomes that were not covered by earlier reviews, specifically by Crowther 2010.

OBJECTIVES

To assess the effects of vitamin K supplementation administered to pregnant women for improving maternal and neonatal outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised (individual and cluster) or quasi-randomised controlled trials assessing the effect of vitamin K supplementation during pregnancy. We will also consider trials presented only as abstracts. We will exclude cross-over trials.

Types of participants

All pregnant women in any stage of their pregnancy and their infants. We will include trials in which pregnant women are a subset of the participants included in the study, if reported in a way that relevant data can be extracted. *This review will exclude* studies in which vitamin K was given to women at risk of imminent preterm birth for preventing neonatal PVH, as this is covered in an existing review by Crowther 2010.

Types of interventions.

We will assess the effects of vitamin K administered orally, intramuscularly or intravenously to pregnant women during any stage of their pregnancy. This review will exclude studies in which vitamin K was administered to women at risk of imminent preterm birth for the prevention of neonatal PVH, as this has already been evaluated in an existing review by Crowther 2010. The intervention group will be pregnant women who have received prenatal vitamin K supplementation alone or in combination with micronutrients, regardless of the dosages, frequency, duration and timing of delivery. The three comparison groups will consist of pregnant women receiving any dosage of vitamin K supplements versus no vitamin K supplements; micronutrients including vitamin K versus micronutrients without vitamin K; and vitamin K versus a placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Perinatal death.
2. Neonatal bleeding.
3. Maternal bleeding incidence, e.g. during pregnancy, intrapartum haemorrhage and postpartum haemorrhage.

Secondary outcomes

Newborns

1. Stillbirth.
2. Neonatal death.
3. Infant death.
4. Subcategories of neonatal bleeding: a) very early onset (nought to 24 hours after birth), b) classic haemolytic disease of the newborn (24 hours to seven days of life), and c) late haemolytic disease or acquired protein C deficiency (APCD) of the newborn (two to 12 weeks of life).
5. Preterm birth (less than 37 weeks of gestation).
6. Low birthweight.
7. Long-term neurodevelopment.
8. Congenital malformation.
9. Severe liver disease: a) induced intrahepatic biliary obstruction, b) cholestasis disease.
10. Malabsorption of vitamin K, e.g. gut resection.
11. Biliary atresia (congenital absence or closure of the major bile ducts, the ducts that drain bile from the liver).
12. *Other morbid conditions*, e.g. *low Apgar score at five minutes*, vitamin K deficiency.

We will summarise any adverse outcomes reported in the included studies.

Mothers

1. Vitamin K deficiency in pregnant women.
2. Anaemia, e.g. megaloblastic anaemia.
3. Hypoprothrombinemia.
4. Thrombocytopenia.
5. Other morbid conditions, e.g. spontaneous abortion.

We will summarise any adverse outcomes reported in the included studies.

Economic data for the use of healthcare resources

Newborns

Special care/intensive care admission; length of hospitalisations; length of other treatment care after hospital discharge; and length of mechanical ventilation.

Mothers

Antenatal hospital admission: utilisation of intensive care units; use of daycare units; and ventilation and dialysis.

Search methods for identification of studies

Electronic searches

We will contact the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register. The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of Embase;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

We will apply no date restrictions on the searches. Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We will also search reference lists of retrieved trials, included trials and relevant review papers.

We will not apply any language restrictions.

We will contact researchers in the area, if needed.

Data collection and analysis

Selection of studies

Two review authors (S Shahrook (SS), N Hanada (NH), K Sawada (KS), E Ota (EO) and R Mori (RM)) will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

Data extraction and management

We will design a form to extract data. For eligible studies, at least two review authors (SS, NH, KS, EO and RM) will extract data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2012) and check for accuracy.

When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (SS, NH, KS, EO and RM) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; the study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias by undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. To take account of design effect, we will adjust their sample sizes using the methods described in the *Cochrane Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs, and if the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Trials with more than two treatment groups

If trials with more than two intervention groups (multi-arm studies) are identified, only directly relevant arms will be included. If studies with various relevant arms are identified, groups will be combined to generate a single pair-wise comparison (Higgins 2011), and the disaggregated data in the corresponding subgroup category will be included. If the control group is shared by two or more study arms, the control group over the number of relevant subgroup categories will be divided to avoid double counting the participants (for dichotomous data, we will divide the events and the total population, and for continuous data, we will assume the same mean and standard deviation but will divide the total population). The details will be described in the 'Characteristics of included studies' tables.

Dealing with missing data

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

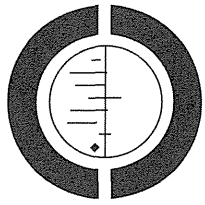
For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

Assessment of heterogeneity

We will assess statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We will regard heterogeneity as

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression (Review)

Churchill R, Moore THM, Furukawa TA, Caldwell DM, Davies P, Jones H, Shinohara K, Imai H, Lewis G, Hunot V



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[Intervention Review]

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression

Rachel Churchill[1], Theresa HM Moore[2], Toshi A Furukawa[3], Deborah M Caldwell[2], Philippa Davies[2], Hannah Jones[4], Kiyomi Shinohara[5], Hissei Imai[6], Glyn Lewis[7], Vivien Hunot[1]

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ABSTRACT

Background

So-called 'third wave' cognitive and behavioural therapies represent a new generation of psychological therapies that are increasingly being used in the treatment of psychological problems. However, the effectiveness and acceptability of third-wave cognitive and behavioural therapy (CBT) approaches as treatment for acute depression remain unclear.

Objectives

1. To examine the effects of all third wave CBT approaches compared with treatment as usual/waiting list/attention placebo/psychological placebo control conditions for acute depression.

2. To examine the effects of different third wave CBT approaches (ACT, compassionate mind training, functional analytic psychotherapy, dialectical behaviour therapy, MBCT, extended behavioural activation and metacognitive therapy) compared with treatment as usual/waiting list/attention placebo/psychological placebo control conditions for acute depression.

3. To examine the effects of all third wave CBT approaches compared with different types of comparators (treatment as usual, no treatment, waiting list, attention placebo, psychological placebo) for acute depression.

Search methods

We searched the Cochrane Depression Anxiety and Neurosis Group Trials Specialised Register (CCDANCTR to 01/01/12), which includes relevant randomised controlled trials from *The Cochrane Library* (all years), EMBASE, (1974-), MEDLINE (1950-) and PsycINFO (1967-). We also searched CINAHL (May 2010) and PSYNDEX (June 2010) and reference lists of the included studies and relevant reviews for additional published and unpublished studies. An updated search of CCDANCTR restricted to search terms relevant to third wave CBT therapies was conducted in March 2013 (CCDANCTR to 01/02/13).

Selection criteria

Randomised controlled trials that compared third wave CBT therapies with control conditions for acute depression in adults.

Data collection and analysis

Two review authors independently identified studies, assessed trial quality and extracted data. Study authors were contacted for additional information when required. We rated the quality of evidence using GRADE methods.

Main results

Four small studies (224 participants) were included in the review. Little information was provided about the process of allocating participants to groups. None of the studies used independent outcome assessors, and evidence suggested researcher allegiance towards the active treatments. The four studies examined a diversity of third wave CBT approaches (extended behavioural activation, acceptance and commitment therapy and competitive memory training) and control conditions. None of the studies conducted follow-up assessments. The results showed a significant difference in clinical response rates in favour of third wave CBT when compared with treatment as usual (TAU) conditions (three studies, 170 participants, risk ratio (RR) 0.51, 95% confidence interval (CI) 0.27 to 0.95; very low quality). No significant difference in treatment acceptability based on dropout rates was found between third wave CBT approaches and TAU (four studies, 224 participants, RR 1.01, 95% CI 0.08 to 12.30; very low quality). Both analyses showed substantial statistical heterogeneity.

Authors' conclusions

Very low quality evidence suggests that third wave CBT approaches appear to be more effective than treatment as usual in the treatment of acute depression. The very small number of available studies and the diverse types of interventions and control comparators, together with methodological limitations, limit the ability to draw any conclusions on their effect in the short term or over a longer term. The increasing popularity of third wave CBT approaches in clinical practice underscores the importance of completing further studies of third wave CBT approaches in the treatment of acute depression, on a short- and long-term basis, to provide evidence of their effectiveness to policy-makers, clinicians and users of services.

PLAIN LANGUAGE SUMMARY

'Third wave' cognitive and behavioural therapies versus treatment as usual for depression

Major depression is a very common condition in which people experience a persistently low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death. Psychological therapies are an important and popular alternative to antidepressants in the treatment of depression. Many different psychological therapy approaches have been developed over the past century, including cognitive-behavioural (CBT), behavioural, 'third wave' CBT, psychodynamic, humanistic and integrative therapies.

In this review, we focused on third wave CBT approaches, a group of psychological therapies that target the process of thoughts (rather than their content, as in CBT), helping people to become aware of their thoughts and to accept them in a non-judgemental way. The aim of the review was to find out whether third wave CBT was effective and acceptable to people in the acute phase of depression. The review included four studies, involving a total of 224 people. The studies examined three different forms of third wave CBT, consisting of extended behavioural activation (two studies), acceptance and commitment therapy (ACT) (one study) and another form of third wave CBT called competitive mind training (one study). Three of the studies compared third wave CBT approaches with treatment as usual control conditions. The fourth study compared ACT with a psychological placebo condition. The results suggested that third wave CBT approaches were effective on a short-term basis in treating depression. However, the quality of evidence was very low because of the small number of studies/participants included in the review, together with the diverse client groups, interventions and control conditions used and possible allegiance of researchers towards the active treatments, making it difficult to draw conclusions with any confidence. It is notable, too, that none of the studies looked at the long-term effect of third wave CBT approaches. Given the increasing popularity of third wave CBT approaches in clinical practice, further well-designed studies should be prioritised to establish whether third wave CBT approaches are helpful in treating people with acute depression.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Third wave CBT versus TAU for depression

Patient or population: depression
Settings: primary, secondary and community care
Intervention: third wave CBT

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Third wave CBT				
Clinical non-response at post-treatment	Study population		RR 0.51 (0.27 to 0.95)	170 (3 studies)	⊕○○○ very low[a,b,c]	
	800 per 1000	408 per 1000 (216 to 760)				
	Moderate					
	689 per 1000	351 per 1000 (186 to 654)				
Treatment acceptability (dropout) at post-treatment	Study population		RR 1.01 (0.69 to 12.3)	224 (4 studies)	⊕○○○ very low[a,b,d,e,f]	
	206 per 1000	208 per 1000 (16 to 1000)				
	Moderate					
	42 per 1000	42 per 1000 (3 to 517)				
Clinical non-remission at post-treatment	Study population		RR 0.77 (0.67 to 0.88)	140 (2 studies)	⊕○○○ very low[a,c,d,f]	
	553 per 1000	734 per 1000 (639 to 839)				
	Moderate					
	538 per 1000	722 per 1000 (628 to 825)				
Depression levels at post-treatment		Mean depression levels at post-treatment in the intervention groups were 1.12 standard deviations lower (1.53 to 0.71 lower)		211 (4 studies)	⊕○○○ very low[a,d,f,g]	SMD -1.12 (-1.53 to -0.71)
Anxiety levels at post-treatment in behavioural activation vs TAU: Beck Anxiety Inventory (BAI)		Mean anxiety levels at post-treatment in the intervention groups was 5.5 lower (10.01 to 0.99 lower)		30 (1 study)	⊕○○○ very low[a,f,h]	
Social adjustment levels at post-treatment: behavioural activation vs TAU: Work and Social Assessment Scale (WSAS)		Mean social adjustment levels at post-treatment in the intervention group was 11.66 lower (17.89 to 5.23 lower)		38 (1 study)	⊕○○○ very low[a,d,e,f]	

*The basis for the **assumed risk** (eg, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk ratio** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Method of sequence generation/allocation concealment unclear. As with all psychological therapy trials, blinding of clinicians/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for therapist qualifications.
[b]Substantial statistical heterogeneity indicated. Diverse study settings and participants (use of student population vs older age population). Treatment length varied from a single session to 12 sessions over 3 months.
[c]Only two third wave CBT approaches included.
[d]High rates of comorbidity with other mood disorders/depressants naturalistically.
[e]One study used a single-session intervention; therefore no dropouts from treatment. One study had 50% dropout rate in TAU group vs 8% in third wave CBT group.
[f]Small to very small sample sizes with wide confidence intervals.
[g]Moderate statistical heterogeneity indicated. Treatment length varied from a single session to 12 sessions over 3 months.
[h]One study limited to single-session intervention with college students reporting mild depression.

BACKGROUND

Description of the condition

Major depression is characterised by persistent low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms, including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death (APA 2000). Somatic complaints are also a common feature of depression, and people with severe depression might develop psychotic symptoms (APA 2000).

Depression is the third leading cause of disease burden worldwide and is expected to show a rising trend over the next 20 years (WHO 2001; WHO 2008). A recent European study has estimated the point prevalence of major depression and dysthymia (a mild long-term form of depression) at 3.9% and 1.1%, respectively (ESEMeD/MHEDEA 2004). As the largest source of non-fatal disease burden in the world, accounting for 12% of years lived with disability (Ustun 2004), depression is associated with marked personal, social and economic morbidity and loss of functioning and productivity and creates significant demands on service providers in terms of workload (NICE 2009). Depression is also associated with a significantly increased risk of mortality (Cuijpers 2002). The strength of this association, even when confounders such as physical impairment, health-related behaviours and socioeconomic factors are taken into account, has been shown to be comparable with, or greater than, the strength of the association between smoking and mortality (Mykletun 2009).

Description of the intervention

Clinical guidelines recommend pharmacological and psychological interventions, alone or in combination, in the treatment of moderate to severe depression (NICE 2009). The prescribing of antidepressants has increased dramatically in many Western countries over the past 20 years, mainly with the advent of selective serotonin reuptake inhibitors and newer agents such as venlafaxine, and antidepressants continue to be the mainstay of treatment for depression in healthcare settings (Ellis 2004; NICE 2009).

Whilst antidepressants are of proven efficacy in acute depression (Cipriani 2005; Gunasekara 2007; Arnold 2009; Cipriani 2009; Cipriani 2009a; Cipriani 2009b), adherence rates remain very low (Hunot 2007; van Geffen 2009), in part because of patients' concerns about side effects and possible dependency (Hunot 2007). Furthermore, surveys consistently demonstrate patients' preference for psychological therapies over antidepressants (Churchill 2000; Riedel-Heller 2005). Therefore, psychological therapies can provide an important alternative or adjunctive intervention for depressive disorders.

A diverse range of psychological therapies is now available for the treatment of common mental disorders (Pilgrim 2002). Psychological therapies may be broadly categorised into four separate philosophical and theoretical schools, comprising psychoanalytic/dynamic (Freud 1949; Klein 1960; Jung 1963), behavioural (Watson 1924; Skinner 1953; Wolpe 1958), humanistic (Maslow 1943; Rogers 1951; May 1961) and cognitive approaches (Lazarus 1971; Beck 1979). Each of these four schools incorporates several differing and overlapping psychotherapeutic approaches. Some psychotherapeutic approaches, such as cognitive analytic therapy (Ryle 1990), explicitly integrate components from several theoretical schools. Other approaches, such as interpersonal therapy for depression (Klerman 1984), have been developed to address characteristics considered to be specific to the disorder of interest.

Increasing interest in the role of cognition gave rise to a 'cognitive revolution' in the field of psychology in the 1970s (Mahoney 1978). The most influential approaches were rational emotive behaviour therapy (Ellis 1962), cognitive behaviour modification (Meichenbaum 1977) and cognitive therapy (Beck 1979). The latter developed as an approach to understanding and treating depression. However, both Beck and Ellis acknowledged the value of behaviour therapy (Richman 1997), and during the 1980s and 1990s, the two approaches were merged to form cognitive-behavioural therapy (CBT).

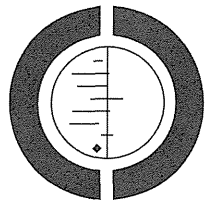
CBT is generally regarded as a family of allied therapies (Mansell 2008) that draw on a common base of behavioural and cognitive models of psychological disorders and utilise a set of overlapping techniques (Roth 2008). In CBT, cognition is central to the treatment of psychological disorders, with emotions and behaviour thought to be mediated by cognitive processes. The fundamental aim of CBT is to identify unhelpful cognitions or 'negative automatic thoughts' derived from long-standing negative beliefs/assumptions about the self, other people or the world. The CBT model proposes that by challenging their meaning and eliciting more realistic thoughts and assumptions, emotions and behaviour can be changed (Clark 1995). An extensive evidence base is available on the effectiveness of CBT, which is recommended as the first-line psychological therapy approach for depression (NICE 2009).

Although the evolution of CBT over the past three decades has tended to overshadow approaches that are more behavioural in nature, evidence supporting purely behavioural approaches has continued to emerge. The findings from Jacobson 1996, a component analysis trial of CBT, suggested that behavioural components alone might work just as well as CBT. These findings revitalised interest in purely behavioural treatments for depression and the development of a more fully realised behavioural intervention based on a contextual approach (Martell 2001).

Prompted by continuing debate in this area, a recent systematic review of 17 randomised controlled trials (RCTs) demonstrated equivalence between CBT and behavioural therapy in terms of depression recovery rates, symptom levels and participant dropout (Ekers 2008). Proponents of a new generation of behavioural therapies, the 'third wave' of CBT (Hayes 2004; Hofmann 2010),

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression (Review)

Hunot V, Moore THM, Caldwell DM, Furukawa TA, Davies P, Jones H, Honyashiki M, Chen P, Lewis G, Churchill R



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[Intervention Review]

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression

Vivien Hunot[1], Theresa HM Moore[2], Deborah M Caldwell[2], Toshi A Furukawa[3], Philippa Davies[2], Hannah Jones[4], Mina Honyashiki [5], Peiyao Chen[5], Glyn Lewis[6], Rachel Churchill[1]

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ABSTRACT

Background

So-called 'third wave' cognitive and behavioural therapies represents a new generation of psychological therapies that are increasingly being used in the treatment of psychological problems. However, the effectiveness and acceptability of third wave cognitive and behavioural therapy (CBT) approaches as a treatment for depression compared with other psychological therapies remain unclear.

Objectives

1. To examine the effects of all third wave CBT approaches compared with all other psychological therapy approaches for acute depression.

2. To examine the effects of different third wave CBT approaches (ACT, compassionate mind training, functional analytic psychotherapy, extended behavioural activation and metacognitive therapy) compared with all other psychological therapy approaches for acute depression.

3. To examine the effects of all third wave CBT approaches compared with different psychological therapy approaches (psychodynamic, behavioural, humanistic, integrative, cognitive-behavioural) for acute depression.

Search methods

We searched the Cochrane Depression, Anxiety and Neurosis Group Specialised Register (CCDANCTR to 01/01/12), which includes relevant randomised controlled trials from *The Cochrane Library* (all years), EMBASE (1974-), MEDLINE (1950-) and PsycINFO (1967-). We also searched CINAHL (May 2010) and PSYNDEX (June 2010) and reference lists of the included studies and relevant reviews for additional published and unpublished studies. An updated search of CCDANCTR restricted to search terms relevant to third wave CBT was conducted in March 2013 (CCDANCTR to 01/02/13).

Selection criteria

Randomised controlled trials that compared various third wave CBT with other psychological therapies for acute depression in adults.

Data collection and analysis

Two review authors independently identified studies, assessed trial quality and extracted data. Study authors were contacted for additional information where required. We rated the quality of evidence using GRADE methods.

Main results

A total of three studies involving 144 eligible participants were included in the review. Two of the studies (56 participants) compared an early version of acceptance and commitment therapy (ACT) with CBT, and one study (88 eligible participants) compared extended behavioural activation with CBT. No other studies of third wave CBT were identified. The two ACT studies were assessed as being at high risk of performance bias and researcher allegiance. Post-treatment results, which were based on dropout rates, showed no evidence of any difference between third wave CBT and other psychological therapies for the primary outcomes of efficacy (risk ratio (RR) of clinical response 1.14, 95% confidence interval (CI) 0.79 to 1.64; very low quality) and acceptability. Results at two-month follow-up showed no evidence of any difference between third wave CBT and other psychological therapies for clinical response (2 studies, 56 participants, RR 0.22, 95% CI 0.04 to 1.15). Moderate statistical heterogeneity was indicated in the acceptability analyses (I^2 = 41%).

Authors' conclusions

Very low quality evidence suggests that third wave CBT and CBT approaches are equally effective and acceptable in the treatment of acute depression. Evidence is limited in quantity, quality and breadth of available studies, precluding us from drawing any conclusions as to their short- or longer-term equivalence. The increasing popularity of third wave CBT approaches in clinical practice underscores the importance of completing further studies to compare various third wave CBT approaches with other psychological therapy approaches to inform clinicians and policymakers on the most effective forms of psychological therapy in treating depression.

PLAIN LANGUAGE SUMMARY

'Third wave' cognitive and behavioural therapies versus other psychological therapies for depression

Major depression is a very common condition, in which people experience persistently low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death. Psychological therapies are an important and popular alternative to antidepressants in the treatment of depression. Many different psychological therapy approaches have been developed over the past century, including behavioural, cognitive-behavioural (CBT), 'third wave' CBT, psychodynamic, humanistic and integrative therapies.

In this review, we focused on third wave CBT approaches, a group of psychological therapies that target the process of thoughts (rather than their content, as in CBT) to help people become aware of their thoughts and accept them in a non-judgemental way. The aim of the review was to find out whether third wave CBT was more effective and acceptable than other psychological therapy approaches for people with acute depression. The review included three studies, involving a total of 144 people. The studies examined two different forms of third wave CBT, consisting of acceptance and commitment therapy (ACT) (two studies) and extended behavioural activation (BA) (one study). All three studies compared these third wave CBT approaches with CBT. The results suggested that third wave CBT and CBT approaches were equally effective in treating depression. However, the quality of evidence was very low because of the small number of studies of poor quality that we included in the review; therefore it is not possible to conclude whether third wave CBT approaches might be more effective and acceptable than other psychological therapies in the short term or over a longer period of time. Given the increasing popularity of third wave CBT approaches in clinical practice, further studies should be prioritised to establish whether third wave CBT approaches are more helpful than other psychological therapies in treating people with acute depression.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *(Explanation)*

Mindfulness-based 'third wave' cognitive and behavioural therapies compared with other psychological therapies for depression

Patient or population: individuals with depression
Settings: primary, secondary and community care
Intervention: mindfulness-based 'third wave' cognitive and behavioural therapies
Comparison: other psychological therapies

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other psychological therapies	Mindfulness-based 'third wave' cognitive and behavioural therapies				
Clinical non-response at post-treatment	Study population		RR 1.14 (0.79 to 1.64)	144 (3 studies)	⊕◯◯◯ very low[a,b,c]	
	427 per 1000	487 per 1000 (337 to 700)				
	Moderate					
	422 per 1000	481 per 1000 (333 to 692)				
Clinical non-response at follow-up: ACT vs other psychological therapies Follow-up: 2 months	Study population		RR 0.31 (0.08 to 1.26)	56 (2 studies)	⊕◯◯◯ very low[a,c,d]	
	351 per 1000	109 per 1000 (28 to 443)				
	Moderate					
	347 per 1000	108 per 1000 (28 to 437)				
Treatment acceptability at post-treatment Dropout rates	Study population		RR 1.12 (0.47 to 2.67)	144 (3 studies)	⊕◯◯◯ very low[a,b,c]	
	134 per 1000	150 per 1000 (63 to 358)				
	Moderate					
	133 per 1000	149 per 1000 (63 to 355)				
Treatment acceptability at follow-up: ACT versus other psychological therapies Dropout rates Follow-up: 2 months	Study population		RR 1.07 (0.1 to 11.23)	56 (2 studies)	⊕◯◯◯ very low[a,c,d,e]	
	135 per 1000	145 per 1000 (14 to 1000)				
	Moderate					
	100 per 1000	107 per 1000 (10 to 1000)				
Non-remission at post-treatment	Study population		RR 0.89 (0.6 to 1.3)	88 (1 study)	⊕◯◯◯ very low[c,f]	
	578 per 1000	514 per 1000 (347 to 751)				
	Moderate					
	578 per 1000	514 per 1000 (347 to 751)				
Depression levels at post-treatment (HAM-D)		Mean depression levels at post-treatment in the intervention groups was 1.85 lower (4.17 lower to 0.68 higher)		113 (3 studies)	⊕◯◯◯ very low[a,b,c]	

Depression levels at follow-up: ACT vs other psychological therapies (HAM-D) Follow-up: 2 months	Mean depression levels at follow-up of ACT vs other psychological therapies in the intervention groups were 4.51 lower (7.47 to 1.55 lower)	49 (2 studies)	⊕◯◯◯ very low[a,c,d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **risk ratio** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]The method of sequence generation/allocation concealment was unclear in two studies. As with all psychological therapy trials, blinding of clinicians/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for treatment fidelity and therapist qualifications.
[b]Only two third wave approaches were included and/or the comparator psychological therapy approaches were limited to CBT.
[c]Sample sizes were small and/or confidence intervals were wide.
[d]Moderate statistical heterogeneity was indicated.
[e]Compared against only one other psychological therapy approach.
[f]As blinding was not possible, the risk of bias in terms of clinician/participants was not achievable. The risk of bias was assessed as high for researcher allegiance and as unclear for treatment fidelity and therapist qualifications.
[g]Only one study provided clinical remission data.

BACKGROUND

Description of the condition

Major depression is characterised by persistent low mood and loss of interest in pleasurable activities, accompanied by a range of symptoms, including weight loss, insomnia, fatigue, loss of energy, inappropriate guilt, poor concentration and morbid thoughts of death (APA 2000). Somatic complaints are also a common feature of depression, and people with severe depression might develop psychotic symptoms (APA 2000).

Depression is the third leading cause of disease burden worldwide and is expected to show a rising trend over the next 20 years (WHO 2004; WHO 2008). A recent European study has estimated the point prevalence of major depression and dysthymia (a mild long-term form of depression) at 3.9% and 1.1%, respectively (ESEMeD/MHEDEA 2004). As the largest source of non-fatal disease burden in the world, accounting for 12% of years lived with disability (Ustun 2004), depression is associated with marked personal, social and economic morbidity and loss of functioning and productivity and creates significant demands on service providers in terms of workload (NICE 2009). Depression is also associated with a significantly increased risk of mortality (Cuijpers 2002). The strength of this association, even when confounders such as physical impairment, health-related behaviours and socioeconomic factors are taken into account, has been shown to be comparable with, or greater than, the strength of the association between smoking and mortality (Mykletun 2009).

Description of the intervention

Clinical guidelines recommend pharmacological and psychological interventions, alone or in combination, for the treatment of moderate to severe depression (NICE 2009). The prescribing of antidepressants has increased dramatically in many Western countries over the past 20 years, mainly with the advent of selective serotonin reuptake inhibitors and newer agents such as venlafaxine, and antidepressants remain the mainstay of treatment for depression in healthcare settings (Ellis 2004; NICE 2009).

Whilst antidepressants are of proven efficacy in acute depression (Cipriani 2005; Gunnar 2007; Arroll 2009; Cipriani 2009a; Cipriani 2009b), adherence rates remain very low (Linton 2007; van Geffen 2009), in part because of patients' concerns about side effects and possible dependency (Hunot 2007). Furthermore, surveys consistently demonstrate patients' preference for psychological therapies over antidepressants (Churchill 2000; Riedel-Heller 2005). Therefore, psychological therapies can provide an important alternative or adjunctive intervention for depressive disorders.

A diverse range of psychological therapies is now available for the treatment of common mental disorders (Pilgrim 2002). Psychological therapies may be broadly categorised into four separate philosophical and theoretical schools, comprising psychoanalytic/dynamic (Freud 1949; Klein 1960; Jung 1963), behavioural (Watson 1924; Skinner 1953; Wolpe 1958), humanistic (Maslow 1943; Rogers 1951; May 1961) and cognitive approaches (Lazarus 1971; Beck 1979). Each of these four schools incorporates several differing and overlapping psychotherapeutic approaches. Some psychotherapeutic approaches, such as cognitive analytic therapy (Ryle 1990), explicitly integrate components from several theoretical schools. Other approaches, such as interpersonal therapy for depression (Klerman 1984), have been developed to address characteristics considered to be specific to the disorder of interest.

Increasing interest in the role of cognition gave rise to a 'cognitive revolution' in the field of psychology in the 1970s (Mahoney 1973). The most influential approaches were rational emotive behaviour therapy (Ellis 1962), cognitive behaviour modification (Meichenbaum 1977) and cognitive therapy (Beck 1979). The latter developed as an approach to understanding and treating depression. However, both Beck and Ellis acknowledged the value of behaviour therapy (Rachman 1997), and during the 1980s and 1990s, the two approaches were merged to form cognitive-behavioural therapy (CBT).

CBT is generally regarded as a family of allied therapies (Mansell 2008) that draw on a common base of behavioural and cognitive models of psychological disorders and utilise a set of overlapping techniques (Roth 2008). In CBT, cognition is central to the treatment of psychological disorders, with emotions and behaviour thought to be mediated by cognitive processes. The fundamental aim of CBT is to identify unhelpful cognitions or 'negative automatic thoughts' derived from long-standing negative beliefs/assumptions about the self, other people or the world. The CBT model proposes that by challenging their meaning and eliciting more realistic thoughts and assumptions, emotions and behaviours can be changed (Clark 1995). An extensive evidence base is available on the effectiveness of CBT, which is recommended as the first-line psychological therapy approach for depression (NICE 2009).

Although the evolution of CBT over the past three decades has tended to overshadow approaches that are more behavioural in nature, evidence supporting purely behavioural approaches has continued to emerge. The findings from Jacobson 1996, a component analysis trial of CBT, suggested that behavioural components alone might work just as well as CBT. These findings revitalised interest in purely behavioural treatments for depression and the development of a more fully realised behavioural intervention based on a contextual approach (Martell 2001).

Prompted by continuing debate in this area, a recent systematic review of 17 randomised controlled trials (RCTs) demonstrated equivalence between CBT and behavioural therapy in terms of depression recovery rates, symptom levels and participant dropout (Ekers 2008). Proponents of a new generation of behavioural therapies, the 'third wave' of CBT (Hayes 2004; Hofmann 2010),