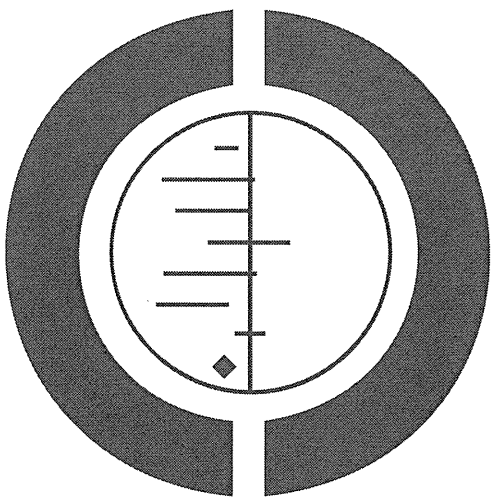
添付資料 9

High dose versus low dose oxytocin for augmentation of labour

High dose versus low dose oxytocin for augmentation of labour (Protocol)

Mori R, Ullman R, Pledge D, Walkinshaw SA



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[Intervention Protocol]

High dose versus low dose oxytocin for augmentation of labour

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ABSTRACT

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

To compare starting dose as well as increment of amount of oxytocin for augmentation in labour to determine whether augmentation by high dose of oxytocin improves labour outcomes and women's satisfaction.

BACKGROUND

Description of the condition

For the majority of pregnant women, once labour has been established, it advances without any intervention required until birth of their babies. However, more than 10% of women have prolonged labour (DOH 2004), and about 40% to 60% of these women have their labour augmented with oxytocin due to slow progress or other reasons in first stage of labour (Gottschall 1997; Impey 2000).

Description of the intervention

Amniotomy is a choice of management for these women, although many women would have already had their membrane ruptured and it is now, according to the latest available evidence, not recommended as routine practice (Smyth 2007). The other option is usually oxytocin infusion. Oxytocin infusion is useful to shorten labour (Wei 2007).

How the intervention might work

Oxytocin infusion is an effective treatment to shorten labour, although great caution is required as fetal distress can occur from hyperstimulation and, rarely, uterine rupture can occur. Previous studies (Jamal 2004; Xenakis 2005) showed a greater effectiveness of high-dose use of oxytocin infusion for augmentation of labour, compared with low-dose oxytocin. The total effect of balancing oxytocin's potential for shortening labour and its adverse effects by use of high dose is still unknown.

Why it is important to do this review

Although there is consensus established that oxytocin infusion is an effective intervention when labour is prolonged, no optimal dose for the intervention has yet to be assessed well. The higher dose can accelerate labour, which may reduce its duration. On the other hand, the higher dose can overstimulate the labouring uterus, which can result in more pain and rupturing. It is critical to understand the balance between the risks and benefits of the intervention.

This review intends to assess the risks and benefits of high and low doses of oxytocin infusion for augmentation of labour, primarily due to delayed first stage of labour.

OBJECTIVES

To compare starting dose as well as increment of amount of oxytocin for augmentation in labour to determine whether augmentation by high dose of oxytocin improves labour outcomes and women's satisfaction.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials. We will include both published or unpublished trials.

Types of participants

Women in labour assessed as requiring augmentation by oxytocin. We will include only women with live fetuses.

Types of interventions

High starting and increment dose (4 micro unit (mU) per minute or more) of oxytocin for augmentation in labour compared with low dose (less than 4 mU per minute). Amount of oxytocin was defined as below:

- high dose: defined as starting dose and increment of equal to or more than 4 mU per minute;
- low dose: defined as starting dose and an increment of less than 4 mU per minute;
- increase interval: between 15 and 40 minutes.

The separation of low and high doses is based on an arbitrary decision.

Types of outcome measures

Primary outcomes

1. Perinatal mortality rate (as defined by authors)
2. Neonatal mortality rate
3. Length of labour
4. Women's satisfaction (measured quantitatively using validated questionnaires)
5. Caesarean section rate

Secondary outcomes

1. Incidence of hyperstimulation
2. Incidence of ruptured uterus
3. Assisted vaginal delivery
4. Diagnosis of chorioamnionitis
5. Incidence of postpartum haemorrhage (blood loss more than 500/1000ml)
6. Use of epidural analgesia
7. Incidence of abnormal cardiotocography (considered only if blindly assessed)
8. Incidence of women's pyrexia
9. Incidence of dystocia
10. Neonatal outcomes of Apgar scores, umbilical cord pH, neurological morbidity, admission to special care baby units

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

Details of the search strategies for CENTRAL and MEDLINE, 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.
We will not apply any language restrictions.

Data collection and analysis

Selection of studies

We will assess for inclusion all potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion, or if required, consult an outside person.

Assessment of methodological quality of included studies

We will assess the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006). Methods used for generation of the randomisation sequence will be described for each trial.

(1) Selection bias (allocation concealment)

We will assign a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomisation, consecutively numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, eg withdrawals, dropouts, protocol deviations)

We will assess completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We will assess blinding using the following criteria:
(A) blinding of participants (yes/no/unclear);
(B) blinding of caregiver (yes/no/unclear);
(C) blinding of outcome assessment (yes/no/unclear).

Data extraction and management

We will design a form to extract data. At least two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion. We will use the Review Manager software (RevMan 2003) to double enter all the data or a subsample.
When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Measures of treatment effect

We will carry out statistical analysis using the Review Manager software (RevMan 2003). We will use fixed-effect meta-analysis

for combining data in the absence of significant heterogeneity if trials are sufficiently similar.

Dichotomous data

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

Continuous data

For continuous data, we will use the weighted 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. If there is evidence of skewness, this will be reported.

Unit of analysis issues

Available case analysis

We will analyse data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we will attempt to restore them to the correct group. If there are not data available on the group to which the participants are allocated, we will not include the data.

Assessment of heterogeneity

We will apply tests of heterogeneity between trials, if appropriate, using the I^2 statistic. If we identify high levels of heterogeneity among the trials (exceeding 50%), we will explore it by prespecified subgroup analysis and perform sensitivity analysis. A random-effects meta-analysis will be used as an overall summary if this is considered appropriate.

Subgroup analyses

We will conduct planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001.

We plan to carry out the following subgroup analyses:

- nulliparous women versus parous women;
- women who had caesarean section before this delivery versus those who had not.

Sensitivity analyses

We will carry out sensitivity analysis to explore the effect of trial quality. This will involve analysis based on an A, B, C, or D rating of selection bias and attrition bias. We will exclude studies of poor quality in the analysis (those rating B, C, or D) in order to assess for any substantive difference to the overall result.
We will carry out sensitivity analysis to explore the effect of trial quality assessed by concealment of allocation, by excluding studies with clearly inadequate allocation of concealment (rated C).

ACKNOWLEDGEMENTS

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

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* *Indicates the major publication for the study*

HISTORY

Protocol first published: Issue 3, 2008

CONTRIBUTIONS OF AUTHORS

R Mori (RM) wrote the first draft of the protocol and R Ullman, D Pledge and S Walkinshaw commented on the draft. RM amended the draft in response to editorial feedback.

DECLARATIONS OF INTEREST

None known.

添付資料　10

Birthweight discordance, risk factors and its impact on perinatal mortality among Japanese twins: data from a national project during 2001-2005

Birthweight Discordance, Risk Factors and its Impact on Perinatal Mortality Among Japanese Twins: Data From a National Project During 2001–2005

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Our aims were to assess the incidence of birthweight discordance of twins, to explore risk factors and its impact on perinatal mortality, and to quantify the risks at different severity of birthweight discordance in Japan, by using a nationwide obstetric database. There were 10,828 pairs of twins, born from 2001 to 2005 recorded in the database of the national Perinatal Health Care Project, fully enrolled. The overall incidence of birthweight discordance was 47.34%. The incidence of mild, severe and extremely severe discordance was 19.26%, 10.21% and 17.87%, respectively. The incidence of birthweight discordance in Japan is much higher than that in other countries, particularly at higher severity level. By linear regression model, our study added independent factors of primiparity ($p < .001$), sex composition ($p < .001$), chorionicity ($p < .001$), gestational age ($p < .001$), and delivery mode ($p < .001$) in determining birthweight discordance percentage. Maternal age and application of assisted reproduction technologies (ART) didn't significantly influence the birthweight discordance. The birthweight discordance is closely associated with gestational age and affected discharge mortality. From 25% of birthweight discordance, risk to discharge mortality tended to significantly increase, suggesting it should be added as a reference for clinical practices.

Keywords: birthweight discordance, gestational age, perinatal mortality, twin, Japan

Birthweight discordance is prevalent among twins and associated with adverse perinatal outcomes including higher risk of fetal and neonatal mortality and morbidity. It suggested that the birth weight discordance is a result of uterine inability to nurture twins equally and this inability is compensated by an adaptive fetal growth restriction of one of the twins causing birthweight discordance (Blickstein et al., 2000).

A twin pair was designated discordant if one was smaller than another by 15% or more. The level of discordance was calculated as a rate of birthweight difference over the birthweight of the heavier twin [discordance percentage = 100 * (birthweight difference/birthweight of heavier twin)]. Severity of birthweight discordance was stratified into the following categories: 15–25%, 25–35%, and 35% or more, which roughly corresponded to mild, severe, and extremely severe discordance, respectively (Blickstein & Lancet, 1998). The percentage difference in birthweight of less than 15% was regarded as the level of concordance.

In Japan, with widespread application of assisted reproductive techniques including ovulation-including agents and in-vitro fertilization, multiple birth rates have increased. Such the phenomenon suggested a tremendous challenge to obstetric management. So far, most studies on this important topic have been implemented in western developed countries, where there also raised some arguments on the association between birthweight discordance gestational age and fetal and neonatal mortality; while the incidence of birthweight discordance as well as its impact on perinatal outcomes among Japanese twins remains unclear. Risk to adverse perinatal outcomes including fetal, neonatal and infant death at different severity of birthweight discordance, as well as its risk factors, needs to be assessed, in order to provide a solid evidence for clinical practices.

The objectives of this study are therefore to assess the incidence of birthweight discordance among

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Japanese twins, to explore risk factors and its impact on perinatal mortality, and to quantify risk to stillborn and discharge mortality at different severity of birthweight discordance, in order to provide an evidence for obstetric management of twining birth.

Methods

The subjects consisted of paired twins recruited from 147 secondary and tertiary hospitals in all 47 prefectures of Japan, which were registered into the Perinatal Health Care Project held by Japan Society of Obstetrics and Gynecology. Most of them are general or university-affiliated hospitals and especially in charge of maternal and infant bodies with high risks, some of them are referred from lower level of health care facilities. The project has been implemented by the Ministry of Health, Welfare and Labour and aims to improve perinatal health care in various medical facilities of Japan, especially to those maternal and neonatal bodies with high risks, with a universal introduction of a medical record registration system, modified clinical guidelines for perinatal complications, and activities of monitoring and evaluating the quality of perinatal cares. Recently, the database of the medical records has been established in nationwide for boosting evidence-based clinical practices and scaling-up the obstetric management throughout the country.

All paired twins born there from January 1, 2001 to December 31, 2005 were recorded in the database at all registered hospitals and enrolled for this study, matched liver-born 10,427 pairs in total, including both normal neonates and those with complications such as TTTS and selective IUGR. Maternal and neonatal data such as maternal parity (primipara or multipara), experience of assisted reproduction (any intervention including in-vitro fertilization and ovulation-including agents), maternal age, maternal disease, mode of delivery (vaginal delivery or cesarean section), gestational age, birthweight, birth order, sex, chorionicity (monochorionic or dichorionic twin), and mortality at the time of discharge were included in the obstetric records and collected for this study. Gestational week was calculated as the number of completed weeks of pregnancy from the investigations of an early dating ultrasound. Maternal disease here inferred to any perinatal complication. Discharge mortality generated the outcome of live or death by the time of discharge from the hospital. Considering the objectives and the current clinical performance in Japan, this study also included stillborn and those weighted less than 500g.

Data analysis was performed by STATA 10.0. Linear regression model and logistic regression model were built to analyze risk factors to birthweight discordance percentage and those to adverse perinatal outcomes including stillborn and discharge morality in one or two of the paired twins, respectively.

This study was approved by Japan Society of Obstetrics and Gynecology. To protect privacy, any individual information such as mothers and infants' name and home address was completely excluded from the obstetric records. The permission of the database use for research was also obtained from Japan Society of Obstetrics and Gynecology.

Results

Incidence of Birthweight Discordance Among Japanese Twins

The average birthweight of heavier babies and lighter babies was 2317.77 g and 1884.61 g, respectively. The average birthweight discordance was 439.85 g. By using 15% birthweight difference as a cut-off point, the overall incidence of birthweight discordance was 47.34%. The incidence of mild, severe and extremely severe discordance was 19.26%, 10.21% and 17.87%, respectively.

The incidence of birthweight discordance, particularly extremely severe discordance (≥ 35%), was much higher in same sex twins (male–male, female–female, 20.98% and 21.83%, respectively) compared to different sex twins (male–female, female–male, 15.1% and 14.77%, respectively; $p < .001$). We made a linear regression model to determine factors affecting birthweight discordance rate. As the result, twins with primiparity ($p = .008$), the same sex ($p < .001$), monochorionicity ($p < .001$), lower gestational age ($p < .001$), and cesarean section ($p < .001$) tended to have more severe birthweight discordance (Table 1).

Risk Factors to Discharge Mortality

The discharge mortality rates at concordance, mild, severe and extremely severe discordance were 1.63%, 2.01%, 4.16%, and 23.01%, respectively.

In logistic regression model for risk factors to discharge mortality, lower gestational weeks ($p < .001$), higher maternal age ($p = .021$), monochorionic ($p < .001$), and higher birthweight discordance percentage ($p < .001$) tended to significantly affect status of discharge mortality (Table 2).

To examine risk to discharge mortality at different severity of birthweight discordance, level of less than 5% of birthweight discordance was set as the reference and odds ratios at every 5% of upper level were calculated. There was no significant difference on discharge mortality at each level below 25%; while from 25% of birthweight discordance, risk to discharge mortality tended to considerably increase (Figure 1).

Gestational Age-Specific Birthweight Discordance

Lower gestational age and preterm birth (less than 37 weeks) showed higher birthweight discordance. At the severity level of concordance, mild discordance and severe discordance, most twins delivered during the 35th to 37th week. The rates of preterm birth at different severity of the discordance were 55.77%, 58.75%, 64.74%, and 76.59%, respectively.

The birthweight curve of heavier baby increased straightly while that of lighter baby increased to the 36th week and then kept flat. Consequently, the birthweight discordance decreased from the 22nd to the

Table 1

Factors Affecting Birthweight Discordance Percentage Among Japanese Twins

Risk factors	Birthweight discordance	95% CI	*p*
Parity			
Primipara	18.89%	(18.49%–19.30%)	.001
Multipara	18.38%	(17.34%–18.92%)	
Assisted reproduction			
Yes	18.81%	(18.37%–19.25%)	.496
No	18.56%	(18.08%–19.04%)	
Maternal age			
< 20 ys	18.51%	(15.35%-21.66%)	.529
≥ 20 ys, < 35 ys	18.75%	(18.37%–19.13%)	
≥ 35 ys	18.55%	(18.37%–19.2%)	
Sex composition			
Same sex	21.05%	(20.49%–21.6%)	< .001
Different sex	17.19%	(16.8%–17.58%)	
Chorionicity			
Monochorionicity	52.40%	(52.13%–52.67%)	< .001
Dichorionicity	18.28%	(17.96%–18.6%)	
Maternal disease			
Yes	18.63%	(18.27%–18.99%)	.623
No	18.72%	(17.95%–19.48%)	
Gestational age			
≤ 36 weeks	20.69%	(20.24%–21.14%)	< .001
> 36 weeks	15.64%	(15.21%–16.08%)	
Delivery mode			
Vaginal delivery	15.94%	(15.67%–16.2%)	< .001
Caesarean delivery	65.46%	(64.85%–66.06%)	

36th week and then rebounded (Figure 2). The birthweight discordance of monozygotic twins exceeded that of their counterparts except during the period from the 33rd and the 38th week, where the tendency was of the opposite.

Discussion

Our study found that the average birthweight of heavier babies and lighter babies was 2317.77g and 1884.61g, respectively, both of which were much less than the average birthweight among twins in the United States (Tan et al., 2005). The birthweight discordance rates of 47.34% were much higher in Japan. Blickstein & Kalish concluded that in general about 75% of twins exhibit less than 15% discordance (concordant), 20% are 15–25% discordant (mildly), and about 5% are more than 25% discordant (severely) (2003). At the rate of 25%, the incidence in Japan was 10.21%, higher than 8.6% in the United States (Tan et al., 2005). Previous studies detected the incidence in some other developed counterparts: in Canada, 53% had 0 to 9% birthweight discordance; 30% had 10 to 19% discordance; 11% had 20 to

Table 2

Risk Factors to Discharge Mortality

Risk factors	Odds ratio	95% CI	*p*
Assisted reproduction (Yes vs. No)	1.121	[0.704–1.159]	.423
Gestational weeks	0.825	[0.803–0.849]	< .001
Maternal disease (Yes vs. No)	1.099	[0.818–1.4744]	.528
Maternal age	0.97	[0.946–0.996]	.021
Chrionicity (Dichrionic vs. monochrionic)	0.641	[0.499–0.823]	< .001
Delivery mode (Cesarean vs. Vaginal)	1.071	[0.802–1.429]	.644
Parity (Primipara. vs. Multipara)	1.038	[0.804–1.333]	.766
Birthweight discordance percentage	31.939	[18.554–54.979]	< .001
Sex composition (Same vs. Different)	1.004	[0.902–1.118]	.937

29% discordance; and 6% had 30% or more discordance (Wen et al., 2005).

Our study added independent factors of primiparity, sex composition, chorionicity, gestational age, and delivery mode in determining birthweight discordance. Maternal age and application of assisted reproduction technologies (ART) didn't significantly influence the birthweight discordance. Some differences rose as well, compared to studies carried out in western countries, for example, showing that the different sex group had significantly higher rate of birthweight discordance than same sex group and that advanced maternal age was positively related to the birthweight discordance (Tan et al., 2005). On the other hand, the mechanism of the impact of maternal age on the birthweight discordance remains unclear, though it has been regarded as one of risk factors to low birth weight and adverse perinatal outcomes among multi-

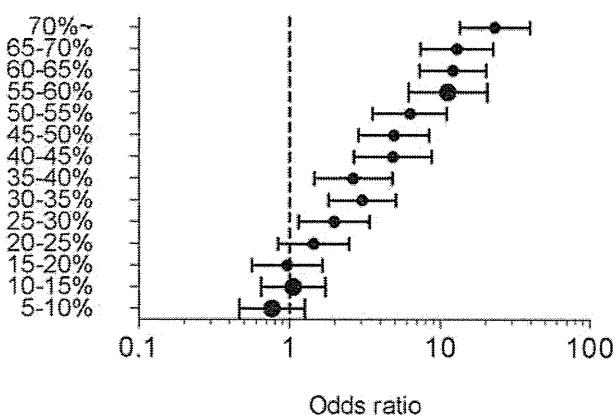

Figure 1

Risk on discharge mortality at different severity of birthweight discordance.

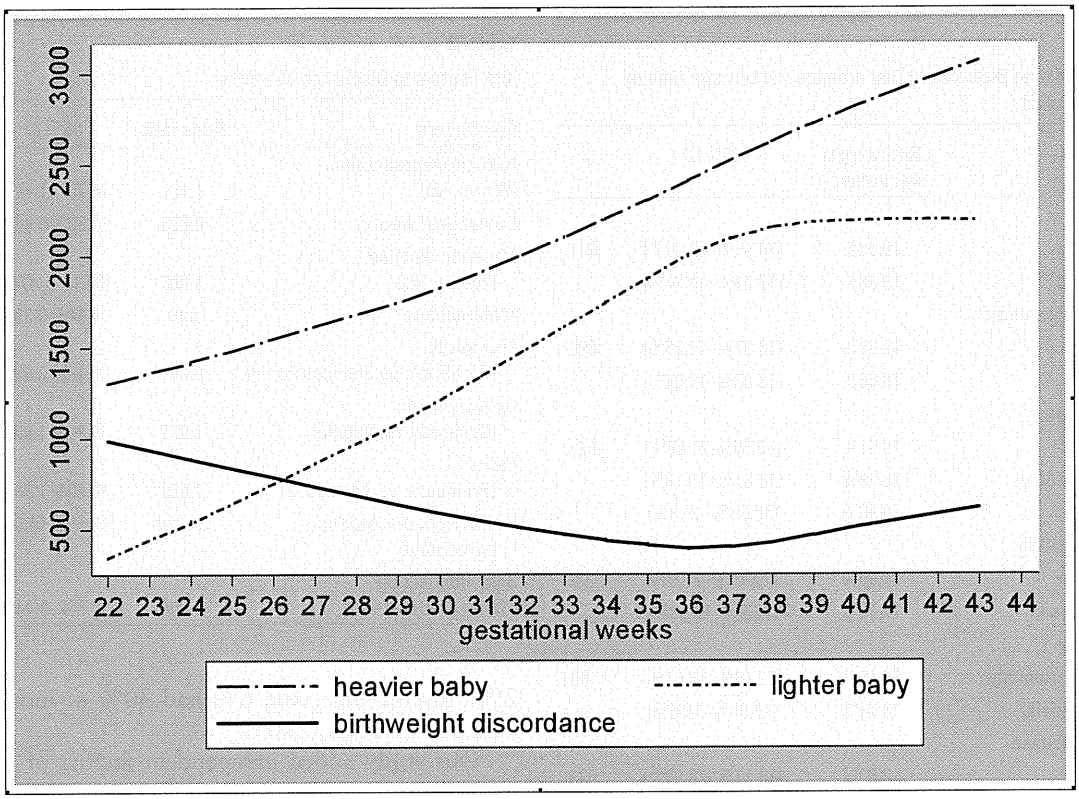

Figure 2
Gestational age-specific birthweight discordance.

ple births (Heish et al., 2010). The difference of epidemiological results between different regions and ethnicities should be highlighted.

The results confirmed that the birthweight discordance is closely associated with gestational age and affected discharge mortality. Preterm birth increased the birthweight discordance severity. With increasing gestational age, the percentage of the birthweight discordance and consequently rates of stillborn and discharge mortality decreased. Moreover, we tested the risks of stillborn and discharge mortality at each 5% of the birthweight discordance percentage, as the results, below 25% of the discordance, the risks didn't changed; conversely, more severe birthweight discordance above 25% leads to significantly increased risks, suggesting severe birthweight discordance of higher than 25% should be added as a reference for obstetric interventions.

In Japan, obstetric interventions are common for multiple births, especially those with high risks to perinatal mortality and morbidity. In current clinical practices, gestational age is precisely calculated, chorionicity is detected at very beginning of pregnancy, and follow-up is implemented closely. The birthweight discordance can be subsequently identified by ultrasound and is accompanied with obstetric interventions. In tertiary and secondary hospitals, most multiple births including twins are the target to fetal growth restriction management and planned delivery at the gestational age approximately up to the 37th week and wellbeing pregnancies after then are out of the target to the planned delivery. Especially those whose discordance exceed 35% are often intervened the planned deliveries at very preterm period, in order to ensure the prognosis. These current practices can be explainable to the phenomenon of the highest discordance at very early gestational age and the lowest one at the age of the 36–37th week in the graph showing gestational age-specified birthweight difference. Meanwhile, the figure also showed the growth arrest of the smaller baby after the 38th week. It may reflect the practice that the growth arrest for more than two weeks is the target to the planned delivery. Taking zygosity into consideration, during the period from the 33rd and the 38th week, when most deliveries implemented, monozygotic twins tended to have less birthweight discordance compared with dizygotic twins. This may be because of that in the current practice, chorionicity is minutely monitored in the follow-up and more positively provided the intervention of preterm delivery.

In conclusion, by application of the large-scale database established in the national project, this study firstly investigated birthweight discordance among Japanese twins. The results are expected to provide evidences to the obstetric interventions in tertiary and secondary hospitals, where have gathered a majority of multiple births including twins, many of them

exposed to high risks of perinatal mortality and morbidity. The incidence of birthweight discordance in Japan is much higher than that in other countries, particularly at higher severity level. Birthweight discordance is closely associated with gestational age and zygosity. By using the large-scale database, birthweight discordance of higher than 25% should be added as a reference for clinical practices.

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添付資料　11

Earlier versus later continuous Kangaroo Mother Care (KMC) for stable low-birth-weight infants: a randomized controlled trial

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REGULAR ARTICLE

Earlier versus later continuous Kangaroo Mother Care (KMC) for stable low-birth-weight infants: a randomized controlled trial

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Abstract

Aim: To examine the effectiveness of earlier continuous Kangaroo Mother Care (KMC) for relatively stable low-birth-weight (LBW) infants in a resource-limited country.

Methods: A randomized controlled trial was performed in LBW infants at a referral hospital in Madagascar. Earlier continuous KMC (intervention) was begun as soon as possible, within 24 h postbirth, and later continuous KMC (control: conventional care) was begun after complete stabilization (generally after 24 h postbirth). Primary outcome measure was mortality during the first 28 days postbirth. This trial was registered with ClinicalTrials.gov, NCT00531492.

Results: A total of 73 infants (intervention 37, control 36) were included. Earlier continuous KMC had higher but no statistically different mortality in the first 28 days postbirth (1 vs. 2; risk ratio, 1.95; 95% CIs, 0.18–20.53; p = 1.00). There were no differences in incidence of morbidities. Body weight loss from birth to 24 h postbirth was significantly less in earlier KMC infants compared with later KMC infants. (−34.81 g vs. −73.97 g; mean difference, 39.16 g; 95% CIs, 10.30–68.03; p = 0.01; adjusted p = 0.02). Adverse events and duration of hospitalization were not different between the two groups.

Conclusion: Further evaluations of earlier continuous KMC including measurement of KMC dose, are needed in resource-limited countries.

INTRODUCTION

Kangaroo Mother Care (KMC) was started in 1978 in Bogotá, Colombia, in response to high mortality and morbidities in neonatal intensive care units for low-birth-weight (LBW) babies (1). In the three decades since, KMC has been introduced all over the world and more than 200 studies pertaining to this practice have been reported internationally.

Kangaroo Mother Care was developed specifically for LBW and/or preterm infants, and it is a method of care in which infants are carried continuously in a skin-to-skin position with the mother to prevent hypothermia, to promote exclusive breastfeeding and to strengthen the mother-infant bond (1,2).

In one review, KMC was identified as one of several cost-effective interventions that can potentially reduce infant mortality and morbidities in LBW infants in resource-limited countries (3). A systematic review claimed that KMC reduces infant morbidities but not mortality, and concluded that evidence was still insufficient to recommend its routine use for LBW infants (4). For healthy term and late preterm infants more than 30 randomized controlled trials (RCTs), most of them small, have provided evidence that early skin-to-skin contact results in better breastfeeding and better mother-infant relationships (5). However, most of these studies were performed in developed countries and only a few mention continuity of care.

An unpublished systematic review by Khanna et al. (6) assessed the effectiveness of skin-to-skin contact initiated within 48 h of birth for LBW babies. Three RCTs fulfilled review criteria, but each study recorded different outcomes and the authors concluded that results pertaining to effectiveness were inconclusive, even if individual studies showed some clinical benefits (7–9). Bergman et al. (8) conducted a RCT of skin-to-skin contact begun within 5 min of birth and continued for 6 h in LBW (1200–2199 g) infants. In this study, earlier KMC showed better physiological stabilization at 6 h of birth. However, there was no information after 6 h postbirth. Moreover, the study was conducted in an upper middle income country, rather than in a resource-limited country (8). Only the trial by Worku et al. (9) performed early initiated continuous KMC for LBW infants in a resource-limited country. In this study, earlier KMC appeared to reduce neonatal mortality; however, as Sloan has pointed out, study group characteristics were not controlled and the analysis was unadjusted (10).

Many LBW babies in resource-limited countries die before they can receive effective interventions. Four million

newborns die each year within 28 days of birth; 25–45% of the deaths occur within 24 h postbirth (11). Sixty to eighty per cent of these deaths are attributed to LBW and one-third is caused by both preterm birth and LBW (12). In the previous KMC studies in resource-limited countries (not including the study by Worku et al.), newborns were enrolled in RCTs only after complete clinical stabilization. This usually took 3–13 (mean or median) days, and more than 90% of deaths occurred before the trials began (13–15). Two small African studies of earlier KMC reported reduction of mortality (16,17). However, they were not RCTs and included various biases.

To reduce neonatal mortality in LBW infants, effective intervention should be begun as soon as possible within 24 h postbirth. The aim of this trial was to assess the hypothesis that earlier initiation (within 24 h postbirth) of continuous KMC reduces neonatal mortality or morbidities with a certain level of safety for relatively stable LBW infants born at a hospital in a resource-limited country.

METHODS

Setting

This trial was conducted at the University Hospital of Mahajanga, Madagascar. Madagascar has been classified as a least developed country (18) and its high neonatal mortality rate is regarded as a serious public health issue (19). Major causes of neonatal death are preterm birth and/or LBW (20,21). KMC was introduced to Madagascar in 2000 and has been widely distributed to referral hospitals throughout the country by the Ministry of Health. The University Hospital of Mahajanga, where we conducted our study, implemented KMC in 2004.

Mahajanga is a coastal city on the northwest part of the island, with 130,000 habitants. The climate is sub-humid, and mean temperatures range from 24.5°C (July) to 27.5°C (December). The University Hospital of Mahajanga is a top-referral hospital in this city, as it has a maternity unit that can perform caesarean sections around the clock and a neonatal unit with several incubators, oxygen and some photo-therapy machines, but no mechanical ventilator.

Participants

All infants born at the University Hospital of Mahajanga were assessed for eligibility to participate in this trial. Eligibility criteria were (i) birth weight under 2500 g, (ii) less than 24 h postbirth, (iii) no serious malformation, (iv) relatively stable clinical condition (oxygen saturation: 95% or more, heart rate: greater than 100 beats per minute, respiratory rate: less than 60 times per minute, capillary refilling time: less than 3 sec), (v) mother and other family members were willing to practice KMC, and (vi) mother and/or family who were to practice KMC were healthy. Exclusion criteria were (i) prolonged apnea (more than 20 sec) and (ii) intravenous infusion.

Eligibility criteria were developed by referring to previous KMC studies (7–9,13–15), practical guide (2) and feasibility at the study site. The first eligibility criterion defined LBW as 'under 2500 g', in accordance with the definition of the World Health Organization (18). The second exclusion criterion, intravenous infusion, was added after piloting, as a result of the objection by Malagasy mothers, families and sometimes hospital staff.

If a baby satisfied all eligibility criteria, we obtained written informed consent from the mother and/or father at the time of enrollment in the study. After obtaining a signature for consent, we performed randomized allocation (Fig. 1).

Sample size

Prescribed sample size at the beginning of the trial or the number of infants that may be registered in the trial during

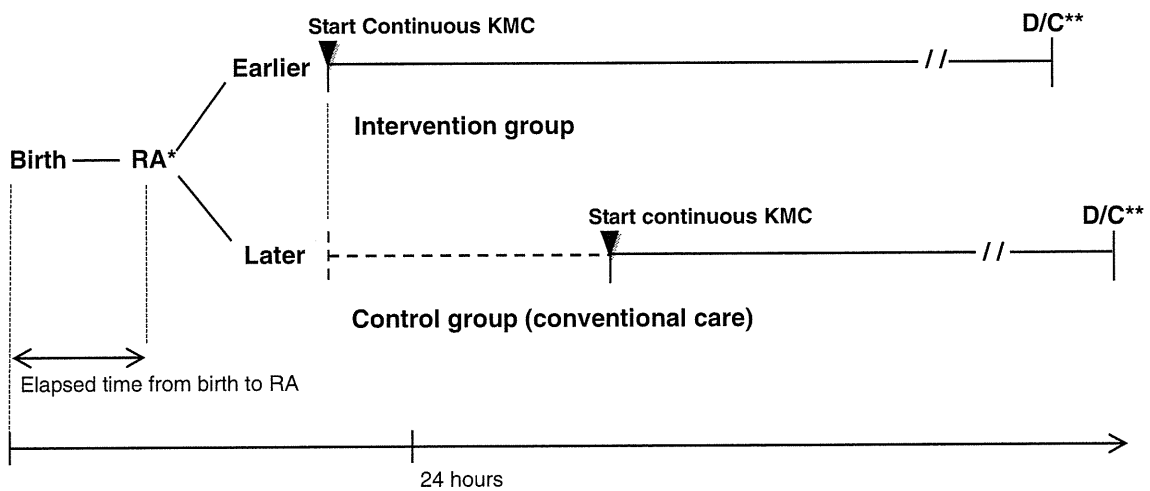

Figure 1 *RA = Randomization, which occurs as soon as the infant is eligible and informed consent has been signed. This can occur at any time during the first 24 h postbirth. When the group assignment is known, the infant can begin either continuous KMC (Earlier group) or continue on Conventional care use an incubator or radiant wormer at first and covered the babies with cotton cloth, lay them beside their mothers. The continuous KMC begin after getting complete stabilization, the timing is depends on the infant and mother's condition (Later group). **D/C = hospital discharge.

1 year was 100 babies. This number was estimated from previous retrospective data in the University Hospital of Mahajanga in 2003 (22) and from medical records just before the trial. Power analysis revealed that 98 participants were necessary to obtain statistical power of 80% with two-sided significance of 5% by Chi-square test for the primary outcome. The sample size was based on an effect size of five in risk ratio and estimated mortality of 25% in the control group.

Randomization

Randomization was performed using the minimization method by software "minim" (23), to ensure balance between earlier KMC group and later KMC group for four factors selected before randomization (birth weight: lower than 2000 g or higher, delivery type: normal delivery (vaginal) or caesarean section, Apgar score at 5 min: 0–6 or 7–10, and elapsed time from birth to randomization: 0–12 h or 12–24 h). After we confirmed that the infant met all eligibility criteria and obtained a signature for informed consent, the newborn was registered in the list of participants and software "minim" automatically provided the random allocation for each participant.

Intervention

Low-birth-weight babies enrolled into the study were randomized into two groups.

The earlier KMC group was instructed to begin KMC as soon as possible within 24 h postbirth. KMC was defined as direct and continuous skin-to-skin contact (without any underwear, except for a diaper, a warm hat and socks for the baby) for as long as possible.

The later KMC group (control) initially followed conventional care. The hospital staff used an incubator or radiant warmer at first, and later covered the babies with cotton cloth and lay them beside their mothers. KMC was begun when the infant and mothers/families were completely settled and ready, which was approximately 48–72 h postbirth.

After initiating KMC, all participants were encouraged by hospital staff to continue KMC for as long as possible during hospitalization and after discharge. Other family members assisted the mother occasionally in performing continuous KMC.

Outcomes

The primary outcome was mortality during the first 28 days postbirth. The secondary outcomes were (i) morbidities during the first 28 days postbirth, (ii) body weight changes (from birth to 24 h, 48 h, day 14 and day 28 postbirth), (iii) adverse events within 28 days postbirth (iv) duration of hospitalization, (v) discharge within 7 days postbirth after birth, and (vi) feeding methods from birth to 24 and 48 h.

A neonatologist independently determined the classification of morbidities based on the interview records and medical charts and monitored the data. The neonatologist was masked to the allocation of participants and did not have any contact with participants. Morbidities were classified as (a) severe infection treated by antibiotics, (b) high fever diagnosed as Malaria, and (c) 'not doing well' (no high fever, vomiting, or diarrhoea, but with anorexia and hypoactivity) and subsequent re-hospitalization within 28 days postbirth.

No previous study has investigated the relationship between earlier continuous KMC and morbidities, although some studies have investigated continuous KMC. Charpak et al. (14) reported infection and re-admission at 41 weeks corrected for gestational age were decreased by continuous KMC (severe infection: RR, 0.69; 95% CIs, 0.43–1.12; nosocomial infection: RR, 0.49; 95% CIs, 0.25–0.93; re-admission: RR, 0.69; 95% CIs, 0.35–1.35). Sloan et al. reported lower respiratory tract disease at 6 months follow-up were decreased by continuous KMC (RR 0.37; 95% CIs, 0.15–0.89) (4,13).

There has been no previous study about body weight change associated with earlier continuous KMC, although one study has investigated its association with intermittent KMC. Chwo et al. reported that infants in the intermittent KMC group reduced body weight to a greater extent than infants in the control group from birth to 48 h and to day 14. By contrast, at day 28 postbirth, infants in the control group had a greater reduction in body weight than infants in the intermittent KMC group (from birth to 48 h: 65.17 g vs. 64.71 g; $p > 0.05$, day14: 854.17 g vs. 893.64 g; $p = 0.824$ day28: 1583.08 g vs. 1560.77 g; $p = 0.907$) (7). Until now, no study has reported the relationship between body weight change during the first 24 h postbirth and earlier continuous KMC.

Adverse events up to 28 days of birth included (a) hypothermia (axillary temperature lower than 35.5°C) during hospitalization, (b) hypothermia (axillary temperature lower than 35.5°C) during outpatient visit, (c) hyperthermia (axillary temperature higher than 37.5°C) during hospitalization, (d) bradycardia (less than 100 beats per minute) and/or tachycardia (more than 180 beats per minute), and (e) prolonged apnea (longer than 20 sec).

In Bergman et al. (8) hypothermia, bradycardia and/or tachycardia, and apnea in the first 6 h of postbirth were reduced to a greater extent in the earlier KMC group than in the control group (hypothermia: $p = 0.006$, bradycardia and/or tachycardia: $p > 0.05$, apnea: $p > 0.05$).

Duration of hospitalization was longer in the earlier KMC group than in the control group in Chwo et al. (earlier KMC = 130 h; control = 105 h), although the difference was not significant ($p = 0.253$) (7). Worku et al. (9) reported the proportion of discharge within 1 week after birth to be almost the same between the earlier continuous KMC group and the control group (RR, 1.02; 95% CIs, 0.90–1.15).

Feeding methods were compared in several studies (13–15). Cattaneo et al. reported that infants provided with continuous KMC was reduced risk that not exclusively breastfeeding at discharge (RR, 0.41; 95% CIs, 0.25–0.68) (15).

Data collection

During hospitalization, data were collected daily through interviews with mother/family and from medical records by a research coordinator. Background data on the baby's

family, including maternal health condition during pregnancy and socio-economic status, were also obtained by the research coordinator through interviews, and entered in questionnaires.

To observe participant health conditions for the first 28 days postbirth, another research coordinator visited all the participants at home on days 14 and 28. This research coordinator was masked to the allocation of participants.

All babies were weighed naked using the same electric scale at the hospital, and the same hand-operated scale at home. Both scales were calibrated routinely. Gestational age was determined by the date of the mother's last menstrual period. If the date of the last menstrual period was uncertain, gestational age was determined in accordance to the results of the New Ballard Score (24). According to Lubchenco's charts, we classified the babies into two categories: appropriate for gestational age and small for gestational age (25).

Statistical analysis

All analyses were based on the intention-to-treat principle. Participant baseline characteristics and outcomes are reported through mean and standard deviation (SD), median (range: minimum and maximum), and frequency (percentage) for comparison between the two groups. Fisher's exact test was used for binary comparisons, and analysis of variance was used to compare continuous data. Risk ratio (RR), mean differences (MD), and their 95% CIs were used to compare incidences or differences in primary and secondary outcomes between the two groups in the study. Differences in body weights were adjusted by birth weight (26). Adjusted analyses were conducted with birth weights, Apgar score, and gender for morbidities and body weight changes in secondary outcomes. Infants within each group were subdivided into subgroups of less than or greater than 2000 g in birth weights, and subgroup analyses were conducted on body weight change from birth to 24 h and from birth to 48 h. Missing data of body weights at 48 h postbirth and days 14 and 28, as a result of lack of measurement or death, were recorded as last observation carried forward. The level of statistical significance was two-sided $p < 0.05$. JMP software version 6.0 (SAS Institute, Cary, NC, USA: http://www.jmp.com/) was used for statistical analyses.

Ethics

The protocol for this study was approved by the Institutional Ethics Committee of the Ministry of Health in Madagascar. This trial was registered with ClinicalTrials.gov, number NCT00531492.

RESULTS

We conducted this study from August 2007 to September 2008. A total of 1126 babies were born at the University Hospital of Mahajanga during those 12 months, and of those, 234 (20.8%) were LBW (Fig. 2). One hundred and twenty-one newborns met the eligibility criteria, and 73 infants underwent randomization. The earlier KMC group (intervention) was 37 infants and the later KMC group (control) was 36 infants. We followed all of them until day 28 postbirth.

Characteristics of the 73 newborn participants were roughly similar between the two groups at birth (Table 1). Distribution in sex was unbalanced.

Mean number of hours postbirth at initiation of KMC was 19.76 h in the earlier KMC group and 33.00 h in the later KMC group. Others helped to perform KMC and feeding conditions were not significantly different between the two groups (Table 2). Feeding condition at day 14 and 28 postbirth were also not different (own mother's milk feeding: day 14: earlier KMC 33/35 vs. later KMC 34/36, day 28: 32/34 vs. 33/33).

The results of the primary and secondary outcomes are shown in Table 3. Of the 37 babies assigned to the earlier KMC group, two died during the first 28 days postbirth. Of 36 babies assigned to the later KMC group, one died during the same period (RR, 1.95; 95% CIs, 0.18–20.53; $p = 1.00$). No mortality occurred in infants with an less than score 7 of Apgar score (at 5 min). The primary causes of mortality in the earlier KMC group were neonatal infection (dead on day 13) and asphyxia (dead during the first 48 h postbirth). The latter died suddenly and unexpectedly during the night. The mother had breastfed the baby a few minutes prior to death, and when the family noticed, the baby lay beside the mother (not in the Kangaroo position). The baby had no major anomalies and showed no danger signs prior to death, and was not from a primiparous pregnancy. We could not perform an autopsy or any additional laboratory tests. Obstructive apnea may have occurred as a result of incorrect breastfeeding technique. The cause of mortality in the later KMC group was maternal-foetal infection (dead on day 17).

Five (13.5%) infants in the earlier KMC group survived with morbidities during the 28 days postbirth. In the later KMC group, 10 (27.8%) survived with morbidities. The earlier KMC group had a reduced frequency of morbidity, but the reduction was not statistically significant (RR, 0.58; 95% CIs, 0.24–1.44; $p = 0.24$). The number of severe infections treated by antibiotics was 3 (8.1%) in the earlier KMC group and 7 (19.4%) in the later KMC group within 28 days postbirth. The number of cases of high fever diagnosed as Malaria was 0 in the earlier KMC group and 2 (5.6%) in the later KMC group. The number of infants 'not doing well' (no fever, vomiting or diarrhoea, but with anorexia and hypo-activity) and re-hospitalized was 2 (5.4%) in the earlier KMC group and 1 (2.8%) in the later KMC group.

Although many outcomes were not statistically different, most favoured earlier continuous KMC (Table 3). Body weight loss from birth to 24 h was significantly reduced in earlier compared with later KMC infants (from birth to 24 h postbirth: −34.81 g vs. −73.97 g; MD, 39.16 g; 95% CIs, 10.30–68.03; $p = 0.02$). Body weight changes from birth to day 14 and 28 were not different in earlier compared with later KMC infants (day 14: 207.78 g vs. 195.64 g; MD, 12.14 g; 95% CIs, −85.23–109.52; $p = 0.98$. day 28: 713.24 g vs. 654.39 g; MD, 58.85 g; 95% CIs, −119.83–237.53; $p = 0.60$).