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A randomised controlled trial of oxytocin 5IU and placebo infusion versus oxytocin 5IU and 30IU infusion for the control of blood loss at elective caesarean section—Pilot study. ISRCTN 40302163

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ABSTRACT

Objective: To compare the blood loss at elective lower segment caesarean section with administration of oxytocin 5IU bolus versus oxytocin 5IU bolus and oxytocin 30IU infusion and to establish whether a large multi-centre trial is feasible.

Study design: Women booked for an elective caesarean section were recruited to a pilot randomised controlled trial and randomised to either oxytocin 5IU bolus and placebo infusion or oxytocin 5IU bolus and oxytocin 30IU infusion. We wished to establish whether the study design was feasible and acceptable and to establish sample size estimates for a definitive multi-centre trial. The outcome measures were total estimated blood loss at caesarean section and in the immediate postpartum period and the need for an additional uterotonic agent.

Results: A total of 115 women were randomised and 110 were suitable for analysis (5 protocol violations). Despite strict exclusion criteria 84% of the target population were considered eligible for study participation and of those approached only 15% declined to participate and 11% delivered prior to the planned date. The total mean estimated blood loss was lower in the oxytocin infusion arm compared to placebo (567 ml versus 624 ml) and fewer women had a major haemorrhage (>1000 ml, 14% versus 17%) or required an additional uterotonic agent (5% versus 11%). A sample size of 1500 in each arm would be required to demonstrate a 3% absolute reduction in major haemorrhage (from baseline 10%) with >80% power.

Conclusion: An additional oxytocin infusion at elective caesarean section may reduce blood loss and warrants evaluation in a large multi-centre trial.

1. Introduction

Caesarean section is one of the most commonly performed major operations in women throughout the world. Rates are escalating, with studies from the United States of America, the United Kingdom and China reporting rates between 20% and 30% [1–4]. There are many possible approaches to performing a caesarean section, the aim being to achieve safe delivery of the infant with a minimum of maternal morbidity. Operative morbidity includes haemorrhage, anaemia, blood transfusion and the risks associated with receiving donor blood products. In severe cases it may result in major obstetric haemorrhage, hysterectomy, admission to an intensive care unit (ICU) or maternal death.

The active management of the third stage at caesarean section has received little attention to date. The value of routine oxytocics in the third stage of vaginal birth has been well established [5] and it has been assumed that these benefits apply to caesarean delivery as well [6,7]. The National Institute of Clinical Effectiveness (NICE) guideline on caesarean section recommends a slow intravenous bolus dose of 5IU of oxytocin following delivery of the infant [8]. This is a lower dose than used previously by many obstetric anaesthetists (10–20IU) [9] and is based on concerns about side effects such as maternal hypotension [10]. Conversely, a conservative approach to the use of oxytocin may increase the risk of haemorrhage.

Intravenous oxytocin has a very short half-life (4–10 min). Therefore, the potential advantage of an oxytocin infusion at caesarean section is that it maintains uterine contractility throughout the surgical procedure and immediate postpartum period, when most primary haemorrhages occur. Several randomised controlled trials have compared intravenous oxytocin with

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oral misoprostol, 15-methyl prostaglandin F2 alpha and carbetocin, reporting limited evidence of benefit with the newer agents [6,11–13]. There has been no trial to date comparing the simpler approach of an intravenous bolus of oxytocin versus an oxytocin bolus and infusion. Both approaches are used in current obstetric practice but there is great variation in the approach of individual clinicians and institutions [14].

This study set out to assess the effects of a 5IU oxytocin bolus and placebo infusion versus a 5IU oxytocin bolus and 30IU infusion on the control of blood loss at elective lower segment caesarean section. We conducted this initial pilot study prior to commencing a definitive multi-centre randomised controlled trial in order to establish the feasibility and acceptability of such a trial.

2. Methods

This was a double blind single site randomised controlled trial carried out at Ninewells Hospital in Dundee, a unit with over 3500 births and a caesarean section rate of 23%. Women booked for an elective lower segment caesarean section were approached and given a patient information pack to read prior to hospital admission. Study participation was discussed on admission and those wishing to participate were recruited with written consent and subsequently allocated randomly to either a placebo infusion or oxytocin infusion in addition to a bolus dose of oxytocin. Women were excluded from participation if there was a placenta praevia, multiple pregnancy, known bleeding disorder or use of anti-coagulant therapy, a past history of a major obstetric haemorrhage or if the surgeon felt that participation was not appropriate for any reason. The criteria for inclusion and exclusion were debated at length with the clinical trials regulatory authority and the research ethics committee. We decided to address blood loss at elective caesarean section in the first instance as recruitment and consent to participation in trials of emergency procedures poses specific ethical difficulties.

A hospital-based clinical trials pharmacist prepared the packs and performed the randomisation. Drug packs were numbered and randomised in the pharmacy in blocks of 10 using the Table of Random Integers in Statistics for Pharmacists. The drug packs were then stored in the labour ward and used in sequence. The oxytocin infusion was prepared by the research midwife by adding 30IU oxytocin to a bag of 500 ml Hartmanns solution. A placebo infusion was prepared and labelled in the same way as the active infusion. The clinicians involved in the care of the patient and the patient herself remained blind to the intervention received. The research midwife took no part in the patient's care or in evaluating the trial outcomes. Each infusion was administered at a rate of 125 ml/h and continued for 4 h following delivery. The approach to anaesthesia and the caesarean section surgical technique were specified in a study protocol (controlled cord traction for delivery of the placenta, non-exteriorisation of the uterus and two-layer closure were specified) and any deviations from the protocol were noted. Cases were only included if regional anaesthesia was used. A full blood count was performed on the second post-operative day.

The aim was to compare the estimated mean operative blood loss and early lochial loss following oxytocin bolus and placebo infusion versus oxytocin bolus and oxytocin infusion. Operative blood loss was estimated by the senior nurse in theatre based on the volume in the suction bottle and the weight of swabs used. We recorded blood loss up until the time the woman was discharged from the theatre recovery ward. We also wished to compare the objective change in haemoglobin and haematocrit pre- and post-operatively, the rate of major haemorrhage (>500 ml and >1000 ml), the use of additional uterotonic agents reflecting atony, the incidence of side effects and the postnatal length of stay for the mother. We aimed to recruit between 75 and 100 women during the 6-month recruitment period.

The results are presented as proportions for categorical data and means and standard deviation for continuous data. Absolute differences in proportions and means are presented with 95% confidence intervals (CIs). Formal statistical tests have not been performed as the pilot study was not designed or powered to detect statistically significant differences in the outcomes measured. Ethics approval for the study was obtained from the multicentre Research Ethics Committee (MREC Edinburgh) and we also obtained Medicines and Health Research Authority (MHRA) approval. All of the investigators attended workshops on good clinical practice (GCP) in the conduct of clinical research.

3. Results

The data on recruitment and randomisation are summarised in the Consort Flowchart (Fig. 1). A total of 55/342 (16%) women were considered non-eligible. For practical reasons (part-time research midwife) only a proportion of the eligible women were approached and of those approached 26/172 (15%) declined to participate with a further 31/287 (11%) delivering prior to the booked date. In total 110 women were correctly randomised to receive either an oxytocin infusion (56) or placebo (54).

The characteristics of the trial participants and operative factors demonstrate that randomisation was largely successful (Tables 1 and 2). However, even small differences in parity, obesity and in particular previous caesarean section rates could have an important impact on the results and we plan to stratify for previous caesarean section in a future multi-centre trial. In general variables should be balanced in a large RCT but if any imbalance remained adjustment would be required using logistic regression techniques. There were very few protocol violations and both anaesthetists and obstetricians adhered to the prescribed surgical and anaesthetic approach. Data collection was largely complete and almost all post-operative blood samples (99%) were taken at the appropriate time.

We noted important potential differences in mean blood loss, rate of major haemorrhage and prolonged post-operative admission between the two groups in favour of the oxytocin infusion arm (Table 3). The rate of major haemorrhage was low (4% placebo) when recorded in theatre and higher when based on haematocrit results (17%). This reflects the well known under estimation of haemorrhage by obstetricians and anaesthetists at the time of caesarean section. A sample size of 1500 women in each arm would be required to demonstrate a 30% reduction in major haemorrhage (3% absolute reduction from baseline 10% based on EBL calculated) with at least 80% power (Table 4).

4. Discussion

This pilot study has demonstrated the feasibility of performing a randomised controlled trial comparing oxytocin bolus versus bolus and infusion for the control of blood loss at elective caesarean section. Several refinements to the study design were incorporated. Eligibility rates and likely recruitment were established. High rates of protocol adherence were confirmed. The results, although limited in determining clinical practice were extremely helpful in establishing sample size calculations for a future definitive study.

A recent review has highlighted the importance of employing techniques routinely at caesarean delivery that are supported by good quality recommendations [15]. The authors noted that those techniques that are not currently supported by quality recommendations such as the management of uterine atony should be researched with adequately powered and designed trials.

These results suggest that the study methodology is feasible and that recruitment and retention to the study are likely to be