Glyceryl trinitrate to reduce the need for manual removal of retained placenta following vaginal delivery: the GOT-IT RCT

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Scientific summary

The GOT-IT RCT

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Scientific summary

Background

Retained placenta following childbirth is a major cause of postpartum haemorrhage, which can ultimately lead to maternal death. The diagnosis is made when the placenta fails to deliver with 30 minutes of active management, or 60 minutes of physiological treatment followed by 30 minutes of active treatment. Women are at greater risk of having a retained placenta if they have previously experienced one in prior childbirth, are aged > 30 years or have a preterm birth or stillbirth. Retained placenta affects approximately 2% of vaginal deliveries, which is approximately 11,000 women in the UK per annum. Major obstetric haemorrhage affects nearly 1 in 180 women and is the most common cause of maternal morbidity.

The current treatment for retained placenta is by a surgical procedure during which the placenta is removed manually by an obstetrician. A hand is inserted into the vagina and the placenta is removed from the uterus. This procedure normally involves transfer of the woman to an operating theatre where it is performed under general, spinal or epidural anaesthesia. Manual removal of placenta is, therefore, a costly procedure in terms of the number of hospital staff that are required. In addition, it can be very stressful for a woman to be separated from her newborn child to undergo the procedure of manual removal of placenta.

Previous studies have suggested that use of a nitric oxide donor may be effective in helping an adherent placenta to be removed from the uterine wall. This is thought to be effective because the nitrate induces relaxation of uterine smooth muscle, thereby allowing the placenta to detach from the uterus. A few small studies have been undertaken involving the use of intravenous glyceryl trinitrate for women who have sustained a retained placenta, as well as using a tablet form of this preparation. Giving glyceryl trinitrate to women to facilitate placenta removal has been reported with varying amounts of success. In addition, small non-randomised or underpowered trials have suggested that administering glyceryl trinitrate sublingually may be a more effective way of aiding placenta removal than the intravenous or tablet preparations. Sublingual glyceryl trinitrate also has a benefit of being more stable at room temperature than either the intravenous form or the tablet form. However, to our knowledge, no large-scale randomised double-blind case-controlled clinical trial of sublingual glyceryl trinitrate for medical management of retained placenta had been undertaken.

Objectives

To determine the clinical effectiveness and cost-effectiveness of sublingual glyceryl trinitrate spray compared with placebo in reducing the need for the manual removal of retained placenta in women after vaginal delivery following the failure of current management.

Methods

The Glyceryl trinitrate fOr reTaIned placenTa (GOT-IT) study was designed as a multicentre randomised controlled trial, with a nested qualitative pilot study and a health economic analysis. All necessary approvals were sought and ethics approval was obtained from the North East – Newcastle and North Tyneside 2 Research Ethics Committee (reference number 13/NE/0339). The study was conducted in 29 obstetric sites in the UK, and the aim was to recruit 1086 women to give the study 90% power with a 5% level of significance. Women in a labour ward setting were considered for the trial if they were diagnosed with a retained placenta, were aged ≥ 16 years, had delivered vaginally, were at > 14 weeks' gestation and were haemodynamically stable. Women were excluded if they were unable to give informed consent, had suspected placenta accreta/increta/percreta or had a multiple pregnancy and had undergone an

instrumental delivery in theatre. We also excluded women who had a known allergy to any constituent of the study medication, had consumed alcohol in the last 24 hours or were currently taking phosphodiesterase inhibitors. Finally, we also excluded women who were known to have other serious conditions (e.g. if they were anaemic or cardiovascularly compromised). Only a clinician could confirm that a potential participant was eligible to be consented to the trial.

Clinicians or midwives who were trained in obtaining informed consent and in study procedures approached women who were considered to be eligible for the trial. Women who were willing to participate could provide either verbal or written consent. If verbal consent was obtained, then written consent was collected as soon as the woman was well enough to provide it. Following the consenting procedure, women were then randomised by a 'next pack off the shelf' method to either the glyceryl trinitrate group or the placebo group. Neither the women nor the labour ward staff were aware of which treatment the women were randomised to because both the study medication and the placebo were packaged identically. Before receiving the study medication, women had a baseline set of clinical observations taken that included measurements of heart rate, blood pressure and temperature. If these were within the correct parameters, women would self-administer the study treatment via a pump-primed canister, which delivered 400 µg of glyceryl trinitrate per metered spray. Two sprays were prescribed sublingually delivering a total dose of 800 µg. Women had their heart rate, systolic blood pressure and temperature recordings repeated at both 5 and 15 minutes following administration of the study treatment. A blood sample was collected to measure haemoglobin level on the first postnatal day. Women were also asked to complete a short questionnaire prior to hospital discharge and again at 6 weeks post discharge.

There were four primary outcomes: clinical, safety, patient sided and economic. The primary clinical outcome was defined as the placenta remaining undelivered 15 minutes after administration of the study treatment and/or delivery being required within 15 minutes of administration of the study treatment because of safety concerns. The primary safety outcome was measured blood loss between administration of the study treatment and transfer to another clinical area or the postnatal ward. The patient-sided outcomes were measured by questionnaires and focused on side-effect profile and satisfaction with treatment. The primary economic outcome was designed to establish if there were net incremental costs (or cost savings) to the NHS using glyceryl trinitrate spray versus standard practice. The study was analysed using an intention-to-treat basis, estimating the effect using odds ratios and 95% confidence intervals. We designed the trial assuming a 50% control (placebo) rate (giving maximum binomial variability) and a 10% absolute reduction in those needing manual removal of placenta (informed by consultation with patients and expert clinicians).

The clinical secondary outcomes that were measured included:

- time from randomisation to the delivery of the placenta
- manual removal of placenta in theatre
- need for earlier than planned manual removal because of clinical concerns
- fall in haemoglobin level of > 15% between recruitment and the first postnatal day
- fall in either diastolic or systolic blood pressure of > 15 mmHg and/or increase in heart rate of > 20 beats per minute (b.p.m.) between baseline and 5 and 15 minutes following administration of study treatment
- requirement for blood transfusion between delivery and postnatal discharge from hospital
- requirement for general anaesthesia
- maternal pyrexia
- sustained uterine relaxation after the placenta has been removed needing treatment with uterotonics.

Economic secondary outcomes studied the mean costs by treatment allocation group and the incremental cost associated with the use of glyceryl trinitrate was estimated using a specified general linear model.

An economic analysis was performed where the primary economic outcome was the net incremental cost (or cost saving) to the NHS of using glyceryl trinitrate spray for the treatment of retained placenta.

Results

A total of 1671 women were screened from October 2014 until July 2017 from 29 participating UK hospitals. Of those 1671 women, 1188 were eligible. Among those 483 patients who were not eligible, 353 were ineligible, 63 declined and 60 were missed, and it was thought not appropriate to recruit seven patients. Among those 1188 patients who were eligible, 63 women declined, 10 women delivered the placenta before there was an opportunity to gain consent and eight women became ineligible prior to consent. Therefore, 543 women were randomised to receive glyceryl trinitrate spray and 564 women were randomised to receive the placebo. There were three postrandomisation exclusions (two in the glyceryl trinitrate group and one in the placebo group) attributable to a violation of baseline observations.

There was no difference in the primary clinical outcome between groups (odds ratio 1.01, 95% confidence interval 0.98 to 1.04; $p = 0.393$). There was no difference in the primary safety outcome of blood loss > 1000 ml between administration of the study drug and transfer to the postnatal ward or other clinical area (odds ratio 1.14, 95% confidence interval 0.88 to 1.48; $p = 0.314$).

The only difference in the patient satisfaction and side-effect profile between the two groups was in the reporting of palpitations/heart racing in the pre-discharge questionnaire. Women in the glyceryl trinitrate group reported significantly more episodes of palpitations and heart racing than those who had received the placebo: 36 (9.8%) in the glyceryl trinitrate group and 15 (4.0%) in the placebo group (odds ratio 2.60, 95% confidence interval 1.40 to 4.84; $p = 0.003$).

There were some differences observed between the two groups in terms of secondary outcomes. More women in the glyceryl trinitrate group demonstrated a drop of 15 mmHg of systolic blood pressure or diastolic blood pressure or an increase in heart rate of 20 b.p.m. between baseline and 15 minutes after receiving the study drug (odds ratio 4.90, 95% confidence interval 3.73 to 6.42; $p < 0.001$). Blood transfusion prior to hospital discharge was also more common in women receiving glyceryl trinitrate than the placebo (odds ratio 1.53, 95% confidence interval 1.04 to 2.25; $p = 0.033$). There was no difference in any of the other secondary outcomes between study groups. There was also no difference in costs to the health service between groups (mean difference £55.30, 95% confidence interval –£199.20 to £309.79).

Conclusions

There was no evidence to suggest that the administration of the glyceryl trinitrate spray to women who were diagnosed with a retained placenta reduced the need for manual removal of placenta. Glyceryl trinitrate spray did not provide an alternative medical management for removal of retained placenta. There was no difference observed in blood loss between the glyceryl trinitrate group and the placebo group, and women who received the glyceryl trinitrate spray rather than the placebo were more likely to report palpitations during their hospital admission. However, by 6 weeks this difference was no longer observed between the two groups. A decrease in blood pressure or an increase in heart rate was significantly more likely to be experienced by those women who received glyceryl trinitrate. This is consistent with the vasodilatory properties of glyceryl trinitrate. Women who received glyceryl trinitrate were more likely to have a blood transfusion than those who received placebo. Finally, the use of glyceryl trinitrate for the treatment of retained placenta was not proven to be cost-effective when compared with standard practice.

Future research is still required to identify suitable medical management of placenta removal as an alternative to the standard care of surgical removal.

Trial registration

The trial is registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry as ISRCTN88609453.

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This report

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