Umbilical vein oxytocin for the treatment of retained placenta (Release Study): a double-blind, randomised controlled trial

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Summary

Background **Retained placenta is associated with post-partum haemorrhage. Meta-analysis has suggested that umbilical injection of oxytocin could increase placental expulsion without the need for a surgeon or anaesthetic. We assessed the effect of high-dose umbilical vein oxytocin as a treatment for retained placenta.**

Methods **In this double-blind, placebo-controlled trial, haemodynamically stable women with a retained placenta for more than 30 min were recruited from 13 sites in the UK, Uganda, and Pakistan. 577 women were randomly assigned by a computer-generated randomisation list stratified by centre to 30 mL saline containing either 50 IU oxytocin (n=292) or 5 mL water (n=285), which was injected into the placenta through an umbilical vein catheter. All trial participants, study workers, and data handlers were masked to individual allocations. The primary outcome was the need for manual removal of the placenta. Analysis was by intention to treat. This study is registered, number ISRCTN 13204258.**

Findings **The primary outcome was recorded for all participants. We detected no difference between the groups in the need for manual removal of placenta (oxytocin 179/292 [61·3%] *vs* placebo 177/285 [62·1%]; relative risk 0·98, 95% CI 0·87–1·12; p=0·84). The need for manual removal was higher in the UK (overall 250/361 [69%]) than in Uganda (90/190 [47%]) or Pakistan (16/26 [62%]). Adverse events did not differ between the two groups.**

Interpretation **Umbilical oxytocin has no clinically significant effect on the need for manual removal for women with retained placenta.**

Funding **WHO, WellBeing of Women, Pakistan Higher Education Commission.**

Introduction

Retained placenta complicates 0·1–2% of deliveries.[1] The rate has increased in Europe since the 1920s and is now nearly ten times that of resource-poor settings.[1] Without prompt treatment, women are at high risk of haemorrhage. At present, treatment is by manual removal of placenta, which needs an operating theatre, a surgeon, and an anaesthetist—facilities that are often unavailable to women in resource-poor settings. As a result, this condition has a case fatality rate of nearly 10% in rural communities.[1] An effective, cheap, low technology treatment is urgently needed.[2]

Ultrasound studies have shown that the usual cause of retained placenta is a failure of retroplacental myometrial contraction.[3] As the retroplacental myometrium contracts and shortens, the relatively inflexible placenta shears off and is expelled. The delivery of oxytocin to the retroplacental myometrium via the umbilical vein and placenta is a low-cost solution. A Cochrane review[4] suggests that this intervention could be beneficial, even though the largest study[5] recorded no benefit and the reduction in rates of retained placenta did not differ significantly to that obtained with expectant management (odds ratio 0·86, 95% CI 0·72–1·01).

When undiluted oxytocin is injected directly into the vein, little of the oxytocin reaches the placental bed.[6] To be effective, at least 30 mL of solution needs to be injected through an umbilical vein catheter—a technique not used in any previous study. Furthermore, analysis of previous trials suggested that studies were more successful when high doses of oxytocin were injected.[1] This finding accords with the outcome of the Release pilot study, for which a dose of 50 IU injected through an umbilical catheter had a success rate of 66% (six of nine attempts; Weeks AD, unpublished data). The Release Study therefore aimed to assess the technique of umbilical vein oxytocin as a treatment for retained placenta, with an injection of 50 IU oxytocin diluted with 25 mL of saline.

Methods

Study setting and participants

This double-blind, placebo-controlled, multicentre trial was undertaken in 13 teaching hospitals in the UK (four sites), Uganda (six sites), and Pakistan (three sites), between Dec 30, 2004, and May 13, 2008. Before the start of the trial, all staff recruiting women into the trial (doctors and midwives) underwent training in the technique of umbilical injection and consent procedures.

Women who had a retained placenta for at least 30 min, who were not bleeding, and who were haemodynamically stable (pulse <100 beats per min and systolic blood pressure >100 mm Hg) were eligible for inclusion. This pragmatic

Lancet 2010; 375: 141–47

Published Online December 8, 2009 DOI:10.1016/S0140-6736(09)61752-9

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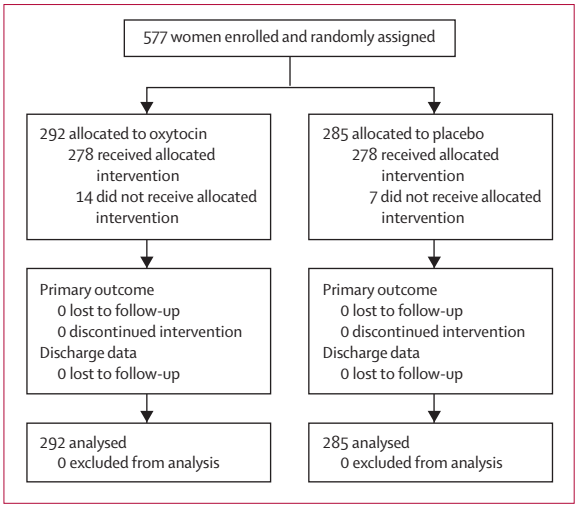

Figure 1: **Trial profile**
The number of women screened was not systematically collected in all centres.

trial allowed for the recruitment of women who delivered in hospital and those referred after delivering at home or in a health centre, if they were haemodynamically stable. We excluded women who had delivered at less than 34 weeks (or whose baby had a birthweight of <2 kg if the gestation was unknown), those whose baby was stillborn, and multiple gestations. Participants were all older than 18 years (or older than 16 years and Fraser competent—ie, deemed to be capable of giving informed consent—in the UK). We also excluded women who had requested a physiological management of the third stage of pregnancy (no early cord clamping, no prophylactic oxytocics, no cord traction or fundal pressure).

The consent procedures were based on consumer-group guidelines[7] for intrapartum recruitment and were developed with their assistance. The details are published elsewhere,[8] but are based on the principle of antenatal information being given to all potential participants, with formal recruitment at the time of the development of the complication. In the UK, all women booking at the participating hospital received information about the study, and posters and newsletters were distributed around the waiting areas in the antenatal clinics. In Uganda and Pakistan, information sheets and posters were put up in labour-ward waiting areas for women who were admitted to the delivery suite. The contact details of local study organisers were made available, as was a website containing the protocol and study information for people who wanted more information. When women developed a retained placenta, the midwife attending to their care briefly discussed the study with them. If they expressed an interest in participation, they received an information leaflet about the study and were asked to provide signed consent. Recruitment and the obtaining of consent were done only by staff trained by the research team.

The trial protocol[9] was approved by the Multicentre Research and Ethics Committee in London, UK; the Makerere University Research and Ethics Committee in Uganda; and the King Edwards Medical University Research Advisory (Ethical) Committee in Pakistan. At WHO it was reviewed by the Research Assessment Panel, the Scientific and Ethical Review Group, and the Committee on Research Involving Human Subjects. The study was registered with the Uganda National Council of Science and Technology and the UK Clinical Research Network, and underwent a successful inspection by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in 2008.

Randomisation and masking

A computer-generated randomisation list was drawn up by staff at the National Perinatal Epidemiology Unit (NPEU), Oxford, UK, with random permuted blocks of 4, 6, or 8, stratified by recruitment centre. Five identical clear vials, each containing 10 IU oxytocin (Alliance Pharmaceuticals, Chippenhan, UK) or 1 mL sterile water, were placed in identical, opaque, sealed trial packs by a commercial organisation (Fisher Clinical Services, Horsham, UK) and consecutively numbered according to the randomisation schedule. Packs were placed in dispensers that were stored in refrigerators in the delivery suites. Thus all trial participants, study workers, and data handlers were masked to individual allocations throughout the study. The randomisation list was held by NPEU, pharmacy at Liverpool Women's Hospital (for unblinding in the event of an emergency), and the trial sponsor only, and was not released until the trial was completed and the database closed. For the interim analyses, only the statistician and the Data Monitoring Committee were informed of each woman's allocation by code (ie, A or B), so that the data could be analysed and examined by group without revealing their identity.

Procedures

After obtaining informed written consent, the researcher took blood samples for a full blood count and blood group and placed a fracture bedpan under the woman's buttocks for collection of blood. The next successive box was taken from the dispenser, and the contents of the five vials were added to 25 mL of saline. A 10F infant feeding tube was then inserted up the umbilical vein until resistance was met. After withdrawal by 5 cm, the 30 mL solution with either 50 IU oxytocin or sterile water was injected up the tube. The cord was then clamped to prevent backflow. Further delivery of the placenta by gentle cord traction was attempted 30 min after umbilical injection if spontaneous delivery had not ensued. If this procedure was unsuccessful, manual removal was undertaken in the usual manner under regional or general anaesthetic. Blood loss was estimated (with the aid of the fracture bed pan) by the attending staff between the time of trial entry and transfer to the postnatal area after completion of the third stage of labour.

	Umbilical oxytocin	Placebo
Recruitment country		
UK	181/292 (62·0%)	180/285 (63·2%)
Uganda	98/292 (33·6%)	92/285 (32·3%)
Pakistan	13/292 (4·5%)	13/285 (4·6%)
Mean age (years, SD)	27·8 (6·3; n=288)	27·9 (6·1; n=276)
Time from delivery to recruitment*		
Median (min, IQR)	65 (46–90; n=271)	63 (45–96; n=265)
>2 h	43/271 (16%)	48/265 (18%)
Hb before delivery of baby		
Mean (g/L, SD)	114·7 (18·4; n=286)	115·3 (17·0; n=281)
<100 g/L	51/286 (17·8%)	40/281 (14·2%)
Epidural use	36/292 (12·3%)	28/285 (9·8%)
Nulliparous	104/288 (36·1%)	87/283 (30·7%)
Gestation		
Mean (weeks, SD)	39·1 (1·6; n=290)	39·0 (1·7; n=283)
<37 weeks	22/290 (7·6%)	22/283 (7·8%)
Birthweight		
Mean (g, SD)	3254 (552; n=290)	3234 (524; n=284)
<2500 g	18/290 (6·2%)	20/284 (7·0%)
Previous CS	21/290 (7·2%)	17/283 (6·0%)

Data are n/N (%), unless otherwise stated. Hb=haemoglobin. CS=caesarean section. *Some chronological data were inaccurate; obvious errors were omitted.

Table 1: **Baseline demographics**

	Umbilical oxytocin	Placebo	Relative risk (95% CI)	p value
Overall				0·84
Manual removal	179/292 (61·3%)	177/285 (62·1%)	0·98 (0·87–1·12)	
By country				0·21*
UK	128/181 (70·7%)	122/180 (67·8%)	1·04 (0·90–1·20)	
Uganda	45/98 (45·9%)	45/92 (48·9%)	0·94 (0·69–1·27)	
Pakistan	6/13 (46·2%)	10/13 (76·9%)	0·6 (0·31–1·16)	
By recruitment centre				0·20*
UK				
Bradford	2/4 (50·0%)	3/5 (60·0%)	0·83 (0·30–2·31)	
Liverpool	57/76 (75·0%)	53/74 (71·6%)	1·05 (0·89–1·23)	
North Staffordshire	16/33 (48·5%)	22/33 (66·7%)	0·73 (0·51–1·04)	
Sheffield	53/68 (77·9%)	44/68 (64·7%)	1·20 (1·00–1·44)	
Uganda				
Arua	4/10 (40·0%)	6/9 (66·7%)	0·60 (0·28–1·26)	
Mbale	5/10 (50·0%)	3/8 (37·5%)	1·33 (0·53–3·23)	
Mbarara	2/3 (66·7%)	2/4 (50·0%)	1·33 (0·46–3·86)	
Mulago	29/54 (53·7%)	28/53 (52·8%)	1·02 (0·75–1·37)	
Nsambya	1/12 (8·3%)	4/10 (40·0%)	0·21 (0·03–1·14)	
Rubaga	4/9 (44·4%)	2/8 (25·0%)	1·78 (0·54–5·78)	
Pakistan				
Lahore	5/12 (41·7%)	8/11 (72·7%)	0·57 (0·30–1·09)	
Muridke	1/1 (100%)	0	..	
Sheikhupura	0	2/2 (100%)	..	
By gestational age				0·40*
≤37 weeks	19/28 (67·9%)	20/34 (58·8%)	1·15 (0·83–1·59)	
>37 weeks	159/262 (60·7%)	157/251 (62·5%)	0·97 (0·68–1·09)	
By previous CS				0·75*
No	169/269 (62·8%)	167/266 (62·8%)	1·00 (0·87–1·14)	
Yes	10/21 (47·6%)	9/17 (52·9%)	0·90 (0·48–1·70)	

CS=caesarean section. *Mantel-Haenszel homogeneity test (to test for consistency of primary outcome across subgroups).

Table 2: **Manual removal of placenta**

Broad-spectrum antibiotics and oxytocics (as per local protocol) were used after manual removal of the placenta. Women had their haemoglobin concentration measured before discharge. The timing of discharge was at the discretion of the clinician who was responsible for the woman's care. After discharge from hospital, researchers checked the inpatient files of the women for details of any post-partum complications. In the UK, the women were sent a questionnaire asking about their satisfaction with the treatment for their retained placenta, breast-feeding, and any problems that they encountered with the treatment 2 weeks after delivery. Serious adverse events were recorded and reported in line with the 2004 UK Medicines for Human Use (Clinical Trials) Regulations.

Outcome measures

The primary outcome measure was the need for manual removal of the placenta after randomisation. A manual removal was defined as the need for the doctor to insert his or her palm beyond the cervix to remove the placenta. If the placenta was detached and within the vagina when a woman was examined in the operating theatre, she was classified as not having undergone a manual removal. Secondary outcome measures were: method of placental delivery; placental removal in theatre; need for general anaesthetic; time from randomisation to delivery of placenta; fall in haemoglobin greater than 10% or 20% from recruitment to 24 h postnatal; estimated blood loss of more than 500 mL and 1000 mL between randomisation and transfer to the postnatal area after completion of the third stage of labour; maternal pyrexia (more than 37·5°C on two successive occasions between 1 and 12 h apart or one reading of more than 38°C in the 24 h after delivery) in the first 24 h post partum; fall in systolic or diastolic blood pressure of more than 20 mm Hg between before injection and 30 min after injection; increase in pulse of more than 20 beats per min between before injection and 30 min after injection; need for blood transfusion between time of delivery and discharge from hospital; readmission to hospital for any reason in the first 2 weeks after delivery for women in the UK group of the study; and satisfaction rates as expressed by the UK women at 2 weeks post partum. Adverse events were: side-effects at time of injection; mother separated from baby for more than 1 h because of retained placenta; surgery to remove retained products of conception before the initial post-partum discharge from hospital (excluding the initial manual removal); antibiotics to treat infection; hysterectomy; and death of newborn infant or mother.

	Umbilical oxytocin	Placebo	Relative risk (90% CI); p value
Placental delivery			
Method of placental delivery			
Spontaneous	20/292 (6·8%)	17/285 (6·0%)	1·15 (0·68–1·94); p=0·96*
Controlled cord traction	79/292 (27·1%)	79/285 (27·7%)	0·97 (0·78–1·22); p=0·96*
Manual removal	179/292 (61·3%)	177/285 (62·1%)	0·98 (0·88–1·10); p=0·96*
Partial removal by controlled cord traction, completed manually	14/292 (4·8%)	12/285 (4·2%)	1·14 (0·60–2·14); p=0·96*
Placental removal in theatre	168/292 (57·5%)	168/285 (58·9%)	0·98 (0·86–1·10); p=0·73
Need for general anaesthetic	35/291 (12·0%)	46/284 (16·2%)	0·74 (0·52–1·05); p=0·15
Median time from randomisation to delivery of placenta (min, IQR)†	95 (45–141; n=272)	85 (50–130; n=269)	p=0·46‡
Blood loss			
Blood loss >500 mL§	99/287 (34·5%)	99/282 (35·1%)	0·98 (0·81–1·19); p=0·88
Blood loss >1000 mL§	31/287 (10·8%)	28/282 (9·9%)	1·09 (0·72–1·63); p=0·73
Fall in Hb >10%¶	185/274 (67·5%)	178/267 (66·7%)	1·01 (0·91–1·12); p=0·83
Fall in Hb >20%¶	94/274 (34·3%)	98/267 (36·7%)	0·93 (0·77–1·13); p=0·56
Blood transfusion‖	43/291 (14·8%)	36/283 (12·7%)	1·16 (0·82–1·64); p=0·47
Haemodynamic changes			
Fall in systolic bp >20 mm Hg**	20/277 (7·2%)	17/268 (6·3%)	1·14 (0·67–1·92); p=0·68
Fall in diastolic bp >20 mm Hg**	9/275 (3·3%)	7/268 (2·6%)	1·25 (0·55–2·84); p=0·65
Increase in pulse >20 bpm**	14/274 (5·1%)	10/267 (3·7%)	1·36 (0·70–2·66); p=0·44
Adverse events			
Reported side-effects at time of injection	18/284 (6·3%)	14/273 (5·1%)	1·24 (0·70–2·18); p=0·54
Mother separated from baby for more than 1 h because of retained placenta	88/291 (30·2%)	76/283 (26·9%)	1·13 (0·90–1·40); p=0·37
Pyrexia§	12/288 (4·2%)	7/283 (2·5%)	1·68 (0·78–3·64); p=0·26
Antibiotics to treat infection¶	38/292 (13·0%)	29/285 (10·2%)	1·28 (0·87–1·87); p=0·29
Surgery to remove retained products¶	2/292 (0·7%)	2/285 (0·7%)	0·97 (0·18–5·03); p=0·98
Hysterectomy¶	0/292 (0%)	1/285 (0·4%)	NA
Death of newborn baby¶	2/292 (0·7%)	3/285 (1·1%)	0·65 (0·14–2·90); p=0·63
Death of mother¶	1/292 (0·3%)	0/285 (0%)	NA

Data are n/N (%), unless otherwise indicated. Hb=haemoglobin. bp=blood pressure. bpm=beats per min. NA=not applicable. *χ^2 test. †Some chronological data were inaccurate; obvious errors were omitted. ‡Mann-Whitney test. §From time of randomisation to completion of third stage. ¶From time of randomisation to first day post partum. ‖Between time of randomisation to time of discharge from hospital post partum. **In first 30 min after injection.

Table 3: **Secondary outcomes**

Statistical analysis

Case report forms were checked for completeness by the local coordinator on the day after randomisation, and missing data were added from the inpatient file in consultation with the local study recruiter. Data not recorded on the data collection forms or the inpatient file (including the missing data from women who did not send back the 2-week satisfaction scores) were marked as absent. Data that were clearly inaccurate (largely chronological data) were excluded. Women were analysed in the group to which they were randomly assigned, irrespective of whether they received an injection. The primary outcome was analysed by intention to treat (no missing data), but missing values were not imputed for secondary outcomes. Data were double entered into a computer database for analysis. All centres were initially analysed together with use of relative risk, Mann-Whitney analysis (for the highly skewed continuous data), or χ^2 tests as appropriate in Intercooled Stata (version 9.0) or SPSS (version 16.0).

Data from the Cochrane review[4] suggested that manual removal of placenta was needed in 61% of women given placebo. A 20% relative reduction in the need for manual removal after intra-umbilical injection of oxytocin compared with placebo was deemed to be clinically significant. To detect a change of this magnitude, 478 women would need to be randomly assigned if the rate of manual removal was 65%, or 572 women if the rate was 60% (power 80%, α=0·05). No drop-outs were expected and it was therefore decided to recruit a minimum of 572 women.

The primary outcome was considered significant if the 95% CI for the relative risk excluded unity. However, since other outcomes were not sufficiently powered, 90% CIs were used for secondary analyses, with an emphasis on the interpretation of confidence intervals. Prespecified subgroups (for the primary outcome only) were country of recruitment, previous caesarean section or not, gestation of more than 37 weeks or not, and recruitment centre. The primary outcome analysis was repeated for each of the subgroups and the results compared with the Mantel-Haenszel homogeneity test.

The independent Data Monitoring Committee reviewed the data (presented as two masked groups) in November, 2006 (data from the first 268 women), and in May, 2007 (data from the first 369 women), and advised the continuation of recruitment. This study is registered, number ISRCTN13204258.

Role of the funding source

WellBeing of Women and the Pakistan Higher Education Commission had no involvement in protocol development, conduct of the study, or data analysis. At WHO, the study was discussed and amended by the Research Assessment Panel, the Scientific and Ethical Review Group, and the Committee on Research Involving Human Subjects. However, they had no other involvement in the conduct or analysis of the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 577 women were recruited and randomly assigned: 292 to oxytocin and 285 to placebo. 361 (63%) were recruited in the four UK sites, 190 (33%) from Uganda, and 26 (5%) from Pakistan.

The recruitment rates were audited at the two largest sites: Liverpool Women's Hospital, UK; and Mulago Hospital, Uganda. In the Liverpool site there were 287 retained placentas between August, 2005, and August, 2006, of which 60 (21%) were recruited to the trial. Of those not recruited, 54 had snapped cords; in 69 the placenta was delivered at between 30 and 45 min, suggesting insufficient time to recruit; four declined to

participate; 57 were not asked (because staff were either not trained to recruit, were too busy, or forgot); and 43 were not eligible. In Mulago Hospital, by contrast, there were 108 retained placentas in 2006, of which 38 (35%) were recruited to the trial. Of those not recruited, six had snapped cords and 64 were not eligible (mostly because of post-partum haemorrhage).

Baseline demographics were similar between the two groups (table 1). The median time from delivery of the baby to recruitment in the two groups was 65 min (table 1). More women had home births or were transferred from outlying units in Uganda (58 of 190; 31%) and Pakistan (11 of 26; 42%) than in the UK (five of 361; 1%).

The primary outcome, the need for manual removal of placenta, occurred in 179 (61%) women in the umbilical oxytocin group and in 177 (62%) in the placebo group (relative risk 0·98, 95% CI 0·87–1·12; table 2). The need for manual removal was considerably higher in the UK than in Uganda or Pakistan (table 2). Mantel-Haenszel homogeneity tests showed no significant treatment differences between country, previous caesarean section, gestation greater than 37 weeks or not, and recruitment centre (table 2).

Analysis of the secondary outcomes and adverse events did not show any difference between women given umbilical oxytocin and those given placebo (table 3). Only 50% (180/362) of those in the UK group returned their 2-week follow-up questionnaires. In this subgroup we noted no significant difference between the groups in number of women with postnatal symptoms, breastfeeding rates, or satisfaction with their childbirth experience (data not shown). One woman in Uganda died because of placenta accreta. When the umbilical oxytocin injection and manual removal did not remove the placenta, she was taken to theatre for a hysterotomy because the expertise for hysterectomy was not available in the centre. This procedure was unsuccessful and she died postoperatively from haemorrhage. In the placebo group, one Ugandan woman with placenta accreta needed a hysterectomy when she bled heavily at attempted manual removal. She required a 4-unit blood transfusion, but otherwise recovered well and was discharged on day 3.

	Total recruits	Time to diagnosis (min)	Umbilical oxytocin		Volume of control (mL)	Double-blind?
			Dose (IU)	Total volume (mL)		
Calderale (1994)[10]	42	30	10	21	21	Yes
Carroli (1998)[5]	193	30	20	20	20	Yes
Frappell (1988)[11]	50	15	10	21	21	Yes
Gazvani (1998)[12]	52	20	20	22	20	No
Hansen (1987)[13]	60	30	10	21	21	Yes
Huber (1991)[14]	141	30	10	21	21	Yes
Kristiansen (1987)[15]	35	20	10	11	10	No
Rogers (2007)[16]	33	45	50	30*	30	No
Selinger (1986)[17]	30	20	10	20	20	Yes
Sivalingam (2001)[18]	35	20	30	30*	30	Yes
Weeks (2009; this study)	577	30	50	30*	30	Yes
Wilken-Jensen (1989)[19]	40	20	100	30	30	Unclear

*Injection given through an intra-umbilical catheter.

Table 4: **Study characteristics of randomised trials of umbilical oxytocin versus placebo**

Discussion

Findings from the Release Study have shown that umbilical vein oxytocin had no clinically significant effect on the need for manual removal of the placenta or any other clinical outcome. Furthermore, the confidence intervals were narrow and did not include the 20% reduction needed for manual removal that was regarded as clinically significant before the study.

The strength of the Release Study is its high quality. It was undertaken under the stringent regulations introduced as part of the European Union Clinical Trials Directive and passed quality checks by the UK MHRA. The study's size and recruitment in diverse settings make the findings highly applicable to the general population. By contrast with previous studies, this trial used a high dose of oxytocin injected through an umbilical catheter—a technique that is known to improve oxytocin delivery to the placental bed.[6] Thus, the reason for lack of efficacy is unlikely to be the delivery of an inadequate oxytocin dose to the placenta.

The striking aspect of the trial data is the international variation in both the incidence of retained placenta and in the need for manual removal after umbilical injection. However, these findings accord with a review[1] in which rates of retained placenta in the UK are seen to be rising with time and seem to be greater in high-resource settings than in low-resource settings. The reasons for this result are not clear, but it could represent the amount of exertion that is put into removal of the placenta by the attendants. In settings in which there are long waits for theatre and in which women are tolerant of pain, there can be many attempts at placental delivery with prolonged cord traction, grasping of vaginal portions of the placenta, and uterine massage. In the UK, by contrast, operating theatres with regional anaesthesia are easily accessible and so the woman does not need to undergo the discomfort of repeated attempts at placental delivery. We believe that this observation increases the importance of double blinding in this clinical scenario and could explain why the analysis of high-quality, double-blind, placebo-controlled trials shows no effect of umbilical oxytocin.

To put the Release Study results into context, we undertook a meta-analysis of all randomised controlled trials comparing umbilical vein injection of oxytocin solution with placebo for the treatment of retained placenta. This update of the Cochrane review[4] included all published studies up to January, 2009, and included an assessment of methodological quality. We included 12 randomised trials (including the Release Study; table 4) with a total of 1288 women. Five studies in which oxytocin

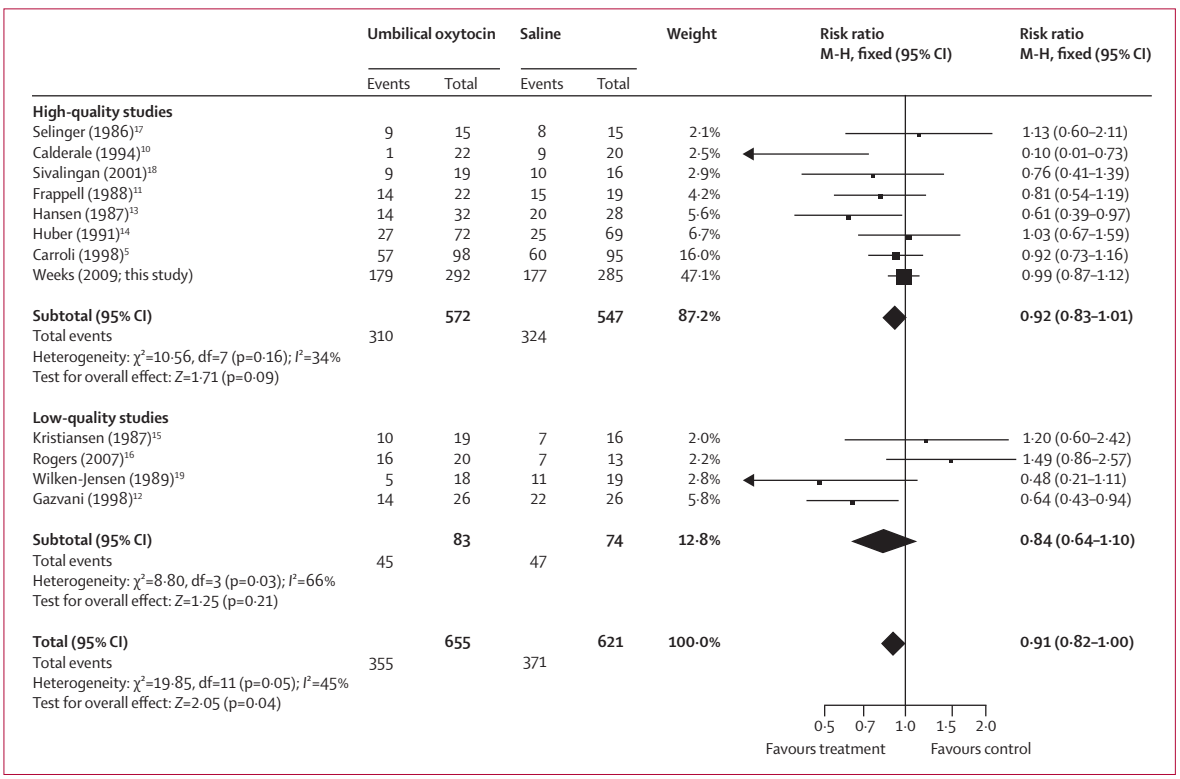

Figure 2: **Meta-analysis of randomised trials of umbilical oxytocin versus saline placebo showing the outcome of need for manual removal**
MH=Mantel-Haenszel homogeneity test.

solution was compared with expectant management showed no significant difference in need for manual removal of the placenta (relative risk 0·87, 95% CI 0·74–1·03) or other outcomes. 12 trials compared oxytocin solution with saline and showed a non-significant reduction in manual removal of the placenta (0·91, 0·82–1·00; figure 2). The test for heterogeneity was of borderline significance (I^2=45%, p=0·05). The eight high-quality studies (containing 87% of the data) were homogenous and showed no difference in need for manual removal of placenta (figure 2). We noted no statistical differences for any of the other outcomes assessed. This meta-analysis, which had previously suggested statistically and clinically significant benefit to umbilical oxytocin injection (odds ratio 0·79, 95% CI 0·69–0·91),[4] now shows no significant difference in the primary outcome, having added the present study. Furthermore, the confidence intervals have narrowed substantially, and the 95% CI for the risk no longer includes the 20% reduction that was deemed to be clinically important.

In its recent guidelines for the management of post-partum haemorrhage, WHO reviewed the data for umbilical oxytocin (including that of the Release Study—at the time unpublished) and argued that it "may be offered".[20] This recommendation was made on the basis that the meta-analysis was of borderline significance and that the intervention was simple, low cost, and had no known side-effects. However, classic evidence hierarchies place a single, well undertaken multicentre study above a meta-analysis of equal size, especially if, as in this case, the meta-analysis of both study design and results is heterogeneous. Three large, high-quality studies (including this study) have now been unable to replicate the results from smaller studies.[5,14] Therefore other management strategies need to be explored. In a busy resource-poor setting, clinicians' time needed to train, administer, and teach this fairly simple but ineffective intervention can be better used elsewhere.

The reason for the lack of efficacy is not clear. In-vitro studies show that the technique provides oxytocin to the placental bed[6] and that oxytocin crosses the placenta.[21] The problem could be that once the oxytocin crosses the syncytiotrophoblast, it enters the retroplacental lakes that drain into the radial veins and then into the uterine vein. Thus the oxytocin might not enter the capillaries where it would be absorbed into the myometrium until its second passage around the body. Additionally, oxytocin could be deactivated by the oxygenase, which is present in large amounts in the placental bed.[22]

Further research is needed to help to define the optimum waiting time before manual removal according to clinical presentation and setting. Furthermore, women with a retained placenta are clearly a heterogeneous group, consisting of those with a trapped placenta, placenta adherens, and placenta accreta. Ultrasound can

aid in the differentiation of the underlying pathological changes, so that therapies can be tailored to the cause.[1] Women with trapped placentas, for example, might respond to the relaxant effect of glyceryl trinitrate.

Contributors

ADW was the chief investigator, had the initial idea for the study, chaired the management group, and wrote the first draft of both the protocol and paper. He is the guarantor for the paper. GA was the trial coordinator in Uganda and a member of the management committee. GV was the international trial administrator. AN was the trial administrator and trainer in Uganda. RG was the trial coordinator in Sheffield and a member of the management committee. TM was the trial coordinator in Pakistan and a member of the management committee. AH was the trial statistician. HJ was the trial administrator in Pakistan. JN and GC did the systematic review with ADW. FF was the principal investigator in Sheffield and a member of the management committee. YR was the principal investigator in Pakistan and a member of the management committee. FM was a study applicant, the principal investigator in Mualgo Hospital, and a member of the management committee. ZA was a study applicant, was a member of the management committee, and had overall supervision of the trial management. All authors reviewed and approved the final version of the report.

Trial management

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Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

Funding for this trial was provided by WHO (HRP project A 35026), WellBeing of Women (W1/03), and Pakistan Higher Education Commission (20-688/R&D/06/1738). We thank all the midwives who recruited to the Release Study throughout the world and the participants who agreed to take part in the study; people who sat on the multiple review committees who helped to refine the study protocol, especially Gill Gyte, Elizabeth Key, and Tina Lavender who worked with us over the complex consent issues; and Alliance Pharmaceuticals who donated and prepared the oxytocin and placebo vials for the trial.

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