ORIGINAL ARTICLE

Is There a Place for Intra-Umbilical Oxytocin for the Management of Retained Placenta?

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Summary

Intra-umbilical injection of oxytocin has been used to hasten placental separation in retained placenta. A randomised controlled trial was done on 35 consequent women who fulfilled the criteria for retained placenta at the Department of Obstetrics & Gynaecology Ipoh Hospital.

Nineteen patients who were recruited into the study group received intraumbilical injection of 30IU oxytocin in 27mls saline. Another 16 patients who were in the control group received 30mls of 0.9% sodium chloride (placebo).

The primary outcome measured was the need for manual removal of placenta (MRP). Nine out of the 19 patients in the oxytocin group required MRP while 10/16 in the control group required MRP. There was a 24% reduction (95% C.I. 0.41 to 1.39) in the need for MRP in the study group compared to the saline group.

Our results indicate that intra-umbilical vein injection of oxytocin is not clinically useful for the removal of a retained placenta.

Key Words: Retained placenta, Manual removal of placenta, Intra-umbilical oxytocin

Introduction

Oxytocin has been used to hasten placental separation and spontaneous expulsion, due to its ability to produce tonic uterine contractions. Despite active management of the third stage of labour with systemic oxytocics postpartum haemorrhage due to retained placenta is a common obstetric complication in developing countries. Postpartum haemorrhage (PPH) constituted 27 - 36% of all maternal deaths in Malaysia between 1991 - 1994[1,2,3,4]. Retained placenta constituted 30.8% of these cases. Complications related to retained placenta contributed to 7.7% of obstetric deaths when perioperative deaths were reviewed in Malaysia between 1994 - 1996[5].

In modern obstetric practice, manual removal of the placenta (MRP) is routinely employed for retained placenta. Perhaps the increasing safety of manual removal with the advent of antibiotics, the availability of blood transfusion and modern anaesthetic techniques have facilitated ready resort to this procedure. However, this conventional treatment is not without risks. Manual removal of the placenta carries a risk of

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infection, anaesthetic complications, haemorrhage and genital tract trauma. A less invasive form of management, may be valuable to reduce the need for operative manual removal.

Umbilical vein injection of oxytocin is a safe procedure in patients who are not actively bleeding. Various techniques have been described with regards to canulation, volume of fluid used and dosage of oxytocin. Pipingas *et al*[6] demonstrated injection via an infant mucus-aspiration catheter introduced along the umbilical vein up to the placental insertion of the cord was effective in producing capillary filling especially when the volume injected was 30ml.

The purpose of this study was to evaluate the role of intra-umbilical oxytocin in the management of retained placenta in a Malaysian hospital, the clinical objective being to find an effective and cheap method to reduce the need for manual removal of the placenta. The aim was also to find a better technique for administration of umbilical vein oxytocin, apart from determining the dose of oxytocin required and the volume of saline required for administration.

The hypothesis tested in this trial was that intra-umbilical vein injection of saline solution containing oxytocin would reduce the need for manual removal of the placenta compared to intra-umbilical vein injection of saline solution alone. The study was performed between September 1998 and May 1999 at the Labour Suite, Ipoh Hospital, Perak, Malaysia.

Materials and Methods

An initial pilot study was performed on six patients from July to September 1998 to perfect the method of intra-umbilical oxytocin administration. During this preliminary study a bolus injection of 30 IU of oxytocin in 27ml of saline was injected into the vein of the umbilical cord in all six patients. Primary and secondary measures of outcome were studied. Having familiarised with the technique of administration of oxytocin, a prospective double blind, randomised controlled trial was done based on the dose stated above.

The study was approved by the hospital ethical committee. All patients who consented to participate and were expected to deliver vaginally were eligible to enter the trial. The umbilical vein infusion of oxytocin or saline was done by the authors to eliminate operator bias.

A protocol for the management of retained placenta was kept in the labour suite and all the personnel involved were familiarised with this at the start of the study. We found no reason to recommend any modification of the trial protocol.

Patient Selection

Randomisation was by the use of a box containing an equal number of envelopes for the Study Group and Control group. Women were allocated to either of the two regimens by opening a sealed opaque envelope which was taken randomly from the box. The envelopes were prepared by two medical officers who were not involved in the study and who kept the personnel involved in the recruitment unaware of the envelope content. Fifty of the envelopes were assigned to patients in the Study Group while another fifty envelopes were assigned to the Control Group.

The inclusion criteria were singleton pregnancies undergoing vaginal delivery and failure to deliver the placenta after 20 minutes of delivering the baby who were least 28 weeks' gestation (196 days). The principal criteria for exclusion were placenta praevia, primary postpartum haemorrhage, snapped umbilical cord, when the patient had an emergency caesarean section in labour, haemodynamically unstable or ill patients, severe anaemia, chorioamnionitis or patients who refused to participate.

Randomisation and Technique

Patients who delivered vaginally and had retained placenta were informed about the study and informed consent was taken from them. They were then randomly allocated to either the oxytocin treated group (Group 1), or the placebo-treated group (Group 2) having fulfilled the selection criteria. The midwife attending the delivery randomly took an envelope from a stock of identical sealed opaque envelopes and opened it. Each envelope carried the instructions to manage retained placenta either with 30IU oxytocin (Syntocinon, 10IU/ml, Sandoz Pharmaceuticals, Petaling Jaya, Malaysia) diluted in 27ml 0.9% sodium chloride solution injected into the vein of the umbilical cord (Group 1) or 30ml of normal saline solution alone into the umbilical vein (Group 2). The midwife then prepared the allocated solution in a 50ml syringe and kept the doctor unaware of the syringe contents. Both solutions were similar in colour and consistency. The trial was thus double blinded in that the patients and the clinicians had no knowledge of the group assignment. An infant feeding tube (size CH06, 2mm diameter, length 40cm, UNO, UnoPlast A/S, Hundested, Denmark) was used to administer the intra-umbilical oxytocin because of ease of insertion of the tube into the umbilical vein. The infant feeding tube was preferred over the umbilical vein catheter as it was much cheaper (RM 2.20 versus RM 6.25 each). The infant mucous-aspiration catheter was not used because of difficulty of attaching a syringe to it. Umbilical vein oxytocin was infused by introducing an infant feeding tube along the umbilical vein to 5cm from the placental insertion of the cord.

The cord was occluded with finger pressure around the catheter during injection. Following injection of the solution the cord was clamped with the catheter in position.

Manual removal was done if the placenta was not expelled within 30 minutes after using intra-umbilical oxytocin or saline, unless heavy bleeding compelled earlier intervention. Intravenous infusion of oxytocin, 40 units in 500ml of saline solution, was begun if bleeding had started. The authors then filled a questionnaire detailing their experience.

All patients for whom an envelope was opened were considered to have entered the trial and were followed up regardless of subsequent management. There were no withdrawals from the trial.

Retained placenta was defined as failure to deliver the placenta 20 minutes after the delivery of the baby. In the questionnaire on obstetric events, maternal age refers to the age of the mother at delivery and parity is defined as the number of previous pregnancies that lasted > 28 completed weeks (196 days from the first day of the LMP).

All patients had the third stage of labour managed actively. Syntometrine 1ml (oxytocin 5 units + ergometrine 0.5mg) was administered intramuscularly either during delivery of the anterior shoulder of the baby or during crowning of the head. In patients with hypertension or cardiac disease Syntocinon 10 units was given instead, by the intramuscular route. In the case of breech vaginal delivery the oxytocic was given soon after delivery of the baby. The umbilical cord was clamped and cut immediately after delivery of the baby. Controlled cord traction was done by the Brandt-Andrews technique[7]. No fundal pressure was applied to the abdomen even if the placenta failed to deliver by controlled cord traction.

Measurement of Blood Loss

Primary postpartum haemorrhage was defined as blood loss from the birth canal of 500ml or more within 24 hours of delivery[8]. Blood loss was measured by collecting all blood and clots in a graduated jug and counting swabs and linen. The commonly employed clinical methods for the estimation of blood loss are often inaccurate or

not feasible because urine, faeces, amniotic fluid and cleaning solution are all mixed on the drapes, kidney dishes and on the floor. Nevertheless, every effort was made for careful assessment of blood loss after delivery and the design of the trial attempted to assure that the potential bias was equal in both arms. Observer bias was minimised by having the authors measure the blood loss in most instances.

Main Outcome Measures

The primary outcome was manual removal of the placenta. Secondary outcomes were the need for blood transfusion, the need for additional uterotonic agents to control postpartum haemorrhage, the incidence of postpartum haemorrhage, the need for uterine curettage and uterine atony.

Statistical Analysis

Data collection, storage and non-parametric analysis were performed with Epi Info Statistical Software (Centres for Disease Control & Prevention, USA and Wold Health Organisation Geneve, Switzerland; Version 6.03, January 1996). Assessment of comparability of groups at trial entry were accomplished by the Fisher exact test and ANOVA. Rates of manual removal of placenta in the oxytocin and control groups were compared by means of the chi-square test. Statistical analysis for the secondary measures of outcome was performed using the Fisher exact test, chi-square test and analysis of variance. Medians and quartiles were calculated for the blood loss for both the oxytocin and control groups; α was set at 0.05 and β at 0.20.

For the primary and secondary measures of outcome, statistical significance was set at the 5% level (95% confidence intervals). When appropriate, results are presented as relative risks and confidence intervals.

Results

The maternal characteristics at trial entry were comparable in both the oxytocin and control group (Table I). The time interval between birth of the baby to entry into the trial averaged just over 30 minutes in both groups. Uterine perforation was not a complication in either group.

When analysis was made for need of manual removal of placenta, 9 of the 19 patients (47%) required MRP compared to 10/16 (62%) in the control group. This was a 24% reduction [(95% C.I. RR 0.76 (0.41 - 1.39)] in the need for MRP in the oxytocin group compared to the saline group. However this difference was not statistically significant ($p>0.05$).

Complications encountered in the trial are listed in (Table II). Maternal complications encountered were postpartum haemorrhage (PPH), need for blood transfusion as a result of PPH, uterine atony, need for additional uterotonic drugs and need for uterine curettage. No significant differences were observed between the two groups. If a morbidly adherent placenta (accreta) was diagnosed, a hysterectomy would have been done and we would have a specimen for histological confirmation. In patients with retained placenta, who needed a uterine curettage, there is a possibility of focal accreta. In the latter, histological evidence would be lacking. We, thus categorised the need for uterine curettage to be a confounding variable. In our context such patients would be coded 'high risk pregnancy' and hospital delivery would be advised in the next pregnancy.

PPH is diagnosed with an estimated blood loss of 500 mls. Blood transfusion is usually not needed unless blood loss is estimated to exceed 1000mls affecting haemodynamic stability. The mean blood loss was 241ml in the oxytocin group compared to 309 in the control group. This difference was not significant ($p>0.05$). Additional uterotonic agents are prescribed in the presence of uterine atony and /or PPH.

Table I
Comparability of Maternal Characteristics at Trial Entry

MATERNAL CHARACTERISTICS	STUDY GROUP (Oxytocin IUVI) (n=19)	CONTROL GROUP (Saline IUVI) (n=16)	p
Maternal age (years)	31 [4.9]	32 [6.8]	0.6
Multiparous	17 (89%)	13 (81%)	0.4
Gynaecology/obstetric history			
Previous retained placenta	2 (11%)	4 (25%)	0.2
Previous curettage	1 (5%)	2 (13%)	0.4
Previous LSCS	3 (16%)	3 (19%)	0.6
Management of third stage			
Syntocinon	2 (11%)	2 (13%)	
Syntometrine	17 (89%)	14 (87%)	
Induction of labour	3 (16%)	4 (25%)	0.4
Time interval (min)*	32 [5.1]	31 [4.9]	0.3

Values are given as n, n (%) or mean [SD]
IUVI = intra-umbilical vein injection
** Time interval between birth of baby and trial entry*

One woman in the control group had PPH of 1500mls but responded to standard resuscitative measures. There were no maternal deaths in the trial.

The inherent inaccuracy of the traditional method of estimating blood loss has been alluded to above. A secondary analysis, stratified by volume of blood loss showed no marked difference between the two groups.

Both the study group and control group were well balanced with regards to the prognostic factors and third stage management before entry into the trial (Table I). The time from birth of the baby to trial entry was similar in the two groups: intra-umbilical saline solution plus oxytocin (mean 32 min + 5.1); and saline solution alone (mean 31 min + 4.9). No uterine perforation was seen in both groups. Compliance was high.

The mean blood loss in the oxytocin group was 241ml, while in the saline group it was 309ml. This difference was not statistically significant ($p>0.05$). The inherent inaccuracy of the traditional method of estimating blood loss has been alluded to above. A secondary analysis, stratifed by volume of blood loss showed no marked difference between the two groups. One woman in the saline group had postpartum haemorrhage of 1500ml. There were no maternal deaths in the study and control groups.

Discussion

The effectiveness of intra-umbilical oxytocin have generally been inconclusive. While some studies show that it is effective, others show otherwise[9] (Table III). Perhaps it was the differences in methodology, which may have confounded the trials. Inconsistencies of the dose of oxytocin, volume of saline infused, together with differences in technique and timing of the injections may well have accounted for the differing results. The dose of umbilical oxytocin varied from 10 IU to 100 IU without reported adverse effects. The injected volume of saline

Table II
Outcome of Women with Retained Placenta in the Two-Treatment Groups

MATERNAL COMPLICATIONS	STUDY GROUP (Oxytocin IUVI) (n = 19)	CONTROL GROUP (Saline IUVI) (n = 16)	p	RR (99% CI)
Blood loss after entry (ml)	241 [± 87]	309 [± 94]	0.06	
Median [Range] ml	200 (150 - 450)	300 (150 - 450)		
Mode ml	200	300		
Blood loss of 500 - 999 ml after entry	2 (11%)	4 (25%)	0.5	
Blood loss > 1000 ml after entry	0	1 (6%)		
Blood transfusion	1 (5%)	1 (6%)	0.7	0.84 (0.06 - 12.42)
Curettage*	1 (5%)	2 (13%)	0.4	0.42 (0.04 - 4.23)
Uterine atony	2 (115)	2 (13%)	0.6	0.84 (0.13 - 5.32)
Need for addiational uterotonic drugs	7 (37%)	10 (63%)	0.2	0.59 (0.29 - 1.19)

Values are given as n, n (%) or menu [SD]
IUVI = intra-umbilical vein injection
** Confounding variable*

ranged between 10 ml and 40ml. The time of oxytocin administration also varied, from 15 minutes to 30 minutes after delivery of the baby.

Although the overall trend is towards a beneficial effect, most studies have failed to demonstrate a significant reduction in the need for manual removal of the placenta with the use of umbilical vein injection of oxytocin. However, this could be because the samples were small and proved underpowered for differences between oxytocin, saline and expectant management.

Given the heterogeneity of the regimens in published literature, it is not surprising that a systematic review[9] shows a relative risk reduction of only 17% which is a modest reduction[10]. The injected volume may play a pivotal role in the process of placental separation. When trials that used 30ml of saline were compared, higher concentrations of oxytocin appeared to have a proportionate reduction in the rates of MRP (Table IV). All trials[9-17] provide no strong evidence of any adverse effects of the umbilical injection of oxytocin.

Reviewing the study of Carroli *et al*[10] in an Argentinean population; our study on Malaysians and Wilken-Jensen *et al*[10] study in an American population; 30 ml of saline appeared to produce consistent rates of manual removal in the control groups, at around 60% (Table IV).

Bider *et al*[13] investigated the efficacy of intra-umbilical prostaglandin F2 alpha injection in women with retained placenta. They suggested

Table III
Effect of Umbilical Vein Oxytocin Infusion Versus 'Other Management' on Manual Removal of the Placenta (Review of Previous Trials)

STUDY[9]	NUMBER OF PATIENTS	OXYTOCIN (IU)	SALINE (ml)	OXYTOCIN CONCENTRATION (IU/ml)
Selinger *et al* (1986)	30	10	20	0.5
Hansen *et al* (1987)	60	10	20	0.5
Frappell *et al* (1988)	41	10	20	0.5
Thiery (1990)	32	10	20	0.5
Huber *et al* (1991)	200	10	20	0.5
Carroli *et al* (1998)	286	20	40	0.5
Kristiansen *et al* (1987)	51	10	10	1
Gazvani *et al* (1998)	81	20	20	1
Present study	35	30	30	1
Wilken *et al* (1989)	37	100	30	3.3
Makkonen *et al* (1995)	109	50	10	5

Table IV
Comparison of Trials with Varying Oxytocin Concentrations

INTERVENTION	SYSTEMATIC REVIEW	OXYTOCIN CONCENTRATION		
		20 IU in 40 ml	30 IU in 30 ml	100 IU in 30 ml
No. of patients		147	35	37
Oxytocin		43 (58%)	9 (47%)	5 (28%)
Saline		43 (59%)	10 (62%)	11 (58%)
P		0.9	0.5	0.1
Relative Risk Reduction	17%	1%	24%	52%

that intra-umbilical vein injection of prostaglandin F2 alpha might be beneficial for treating retained placenta. However, a systematic review[9] found no significant differences between intra-umbilical oxytocin and intra-umbilical prostaglandin with regards to rates of manual removal of placenta, the interval of injection to delivery of placenta, blood loss, fever, abdominal pain and oxytocin augmentation. Since there is a marked difference in the price of prostaglandins and oxytocin, oxytocin is probably the better alternative in Malaysia.

We are not aware of any other study where umbilical vein cannulation with a size 6 infant feeding tube for the administration of oxytocin has been used as recommended by Pipingas *et al*[6] in evaluating the efficacy of intra-umbilical vein oxytocin. However in contrast to the latter's postulation, no beneficial effect of intra-umbilical vein administration of oxytocin is seen on the relative frequency of manual removal of the placenta or on the amount of blood loss in our study. Our reason for using 30IU of oxytocin was to get a satisfactory concentration of 1IU/ml.

However, from the results of this study future studies should probably consider increasing the concentration of oxytocin to 100IU in 30ml of saline.

Our limitation was that the sample size was small. Therefore the study may have proved underpowered for differences between oxytocin and saline. However from the results of this preliminary study a few basic questions have been answered, namely the method of administration, the dose of oxytocin and the amount of saline to use. A coordinated approach would ensure that common methodology - the volume of saline in which oxytocin is injected and the method of infusion - is used and endpoints are chosen so that any future meta-analyses can be simply carried out. There is also scope for further research in the umbilical vein injection of prostaglandins[13]. Such data will be a great asset to midwives dealing with retained placenta in developing countries.

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