Report

Randomised Controlled trial comparing the effects of oxytocin 5units IV bolus vs oxytocin 5units IV infusion on cardiac output during Caesarean section.

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Sponsor

Liverpool Women's Hospital Foundation NHS Trust

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Short title (<70 characters):

Effect on cardiac output of oxytocin bolus vs. infusion.

Aims of the study

1. To determine whether Oxytocin 5 units given by an IV infusion causes lesser haemodynamic disturbance than by IV bolus.
2. To examine the effect of the two methods on intraoperative uterine contractility.
3. To see if the different methods of administration produce a measurable effect on perioperative blood loss.

Scientific Background

Clinical problem

Oxytocin is a drug routinely used in obstetrics to aid uterine contraction. Traditionally 10 units was given as an IV bolus after delivery of the baby at Caesarean section.

Oxytocin causes reduced systemic and pulmonary vascular resistance and increased cardiac output seconds after injection [1-4] and is known to cause arrhythmias [8]. These effects can be detrimental in patients with hypovolaemia or cardiac disease who are unable to mount compensatory responses and therefore are at risk of haemodynamic collapse after oxytocin bolus.

The CEMD report [5] emphasized the profound haemodynamic changes that 10 units of oxytocin can cause and made recommendations that the drug should be given slowly in a dose of not more than 5 IU.[5] Since then 84% of UK anaesthetists have changed their practice and started using 5 units[6]

The cardiovascular effects seen with oxytocin bolus administration occur transiently and are not readily detected using conventional non-invasive blood pressure monitoring. In 2007, Thomas[7] used intra-arterial pressure monitoring to compare changes in blood pressure following 5 units of oxytocin. In this unblinded study, one group of patients, received as slow bolus given over 10 seconds and the other group received the oxytocin as an infusion over 5 minutes. The mean arterial pressure decreased by 27 (7.6)mmHg in the bolus group compared with 8 (8.7) mm Hg in the infusion group. There were no differences in the estimated blood loss between the two groups. This study suggested that a slower rate of administration may be associated with greater cardiovascular stability. However, the study itself was not blinded and the authors did not monitor cardiac output.

The LiDCOplus system is used in the intensive care unit and operating theatre to measure cardiac output in high risk patients[10,11]. It derives cardiac output measurements by computing pulse power from the arterial waveform generated by an intra-arterial pressure monitor. We have recently used this system at the Liverpool Women's Hospital to study patients at term pregnancy. Our work revealed significant changes in Systemic vascular resistance (SVR) and Cardiac output (CO) in response to 5 units of oxytocin[9]. We now plan to expand this work further by conducting a double blind RCT to examine what cardiovascular changes are produced with different rates of oxytocin administration. Our study aims to refute the null hypothesis that 5 units of oxytocin will cause the same change in mean arterial pressure when given over 10 seconds as a bolus or over 5 minutes as an infusion. The anaesthetist and the researchers will remain blinded to the rate of oxytocin infusion, to exclude bias due to changes in rate of intravenous fluid administration or use of sympathomimetic drugs by the anaesthetist.

In our previous work, we calibrated the LiDCOplus system using a Lithium Dilution method. This study aims to measure relative rather than absolute values of cardiac output and systemic vascular resistance and will therefore not require calibration. This enables quicker on-table application of monitoring and avoids need for Lithium administration.

This trial will be conducted in compliance with the protocol, Good Clinical Practice and Medicines and Healthcare products Regulatory Authority (MHRA) regulations.

References

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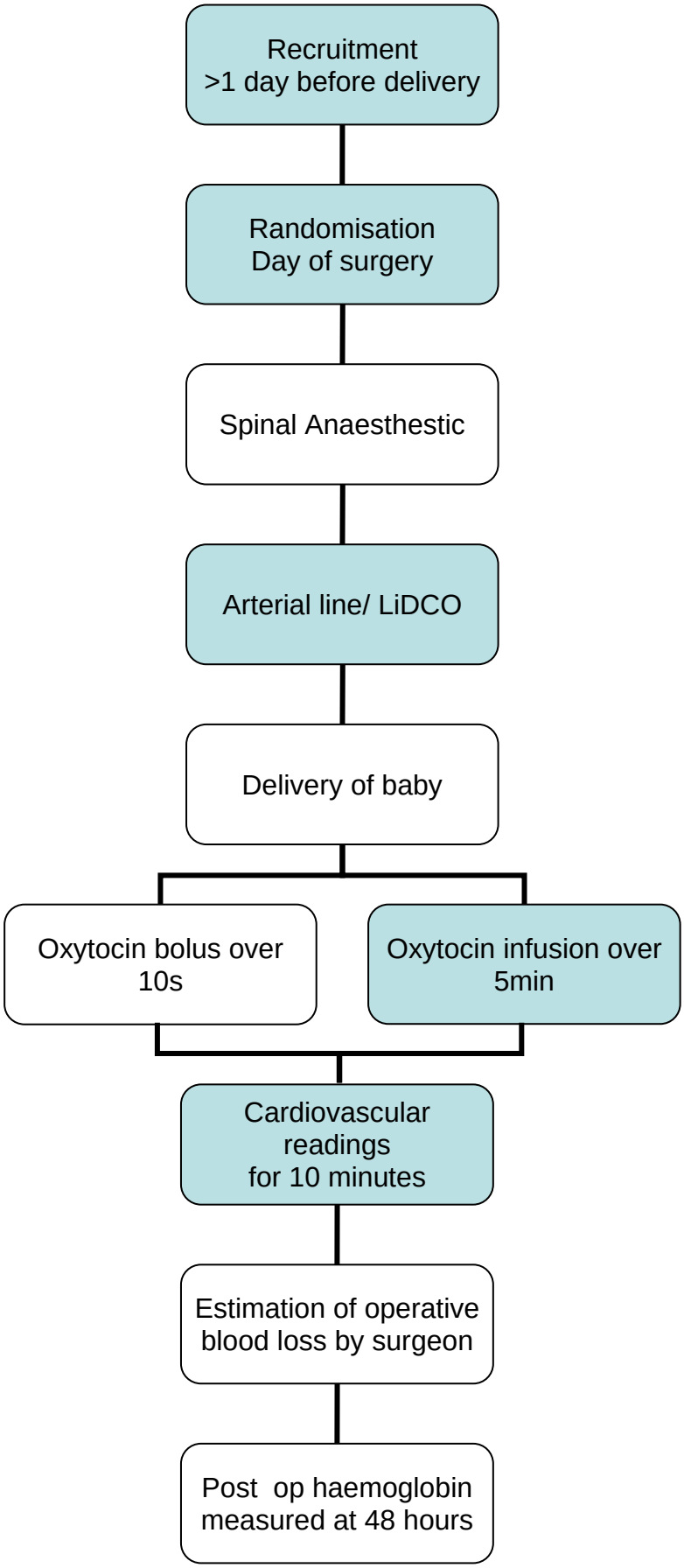
Method

Study Design



Double blind randomised controlled trial, using a sealed envelope method of patient group allocation.

Patients and investigators will not be aware which treatment they has been used and the results will be assessed by an investigator who is blinded to patient treatment group.

Informed consent will be obtained when the patient attends the obstetric pre op clinic and the patient information leaflet will be distributed at this time.

On the day of surgery the patients will arrive in theatre and an arterial line will be placed in addition to intravenous cannula. The LiDCO^{TM} haemodynamic monitoring will be connected in theatre. A standard 2 litre fluid load will be given before the spinal is performed as per usual practice in our hospital.

Ephedrine boluses will be given as a rescue medication to keep the MAP within 20% of the preoperative values, any adverse reactions to ephedrine will be recorded in the same way as reactions to oxytocin. We will note time of each bolus as a data marker and calculate total quantity of ephedrine administered. Surgery will commence when a block of height of T4 bilaterally to cold is achieved.

Oxytocin is routinely administered to aid uterine contraction by anaesthetists during Caesarean section. 5 units represents 0.5 ml of a 10 units/ml solution so it is common practice amongst anaesthetists to dilute oxytocin with 0.9% sodium chloride for precise dose administration. Once the ampoule is opened, oxytocin is not stable for more than 12 hours. Oxytocin is therefore best prepared at the point of administration in the operating theatre. The syringes will be prepared by an independent anaesthetist, according to the patient allocated group contained in the sealed envelope.

	5 ml syringe	20 ml syringe
Group B	5 units oxytocin with 0.9% sodium chloride to 5 ml	18 ml 0.9% sodium chloride
Group I	5 ml 0.9% sodium chloride	6 units oxytocin with 0.9% sodium chloride to 18 ml

The 20 ml syringe contains 18 ml of fluid to allow 3 ml of solution to be flushed through the giving set so the patient will receive a total of 15 ml of study solution.

After delivery, the contents of two syringes will be administered. The 5 ml syringe will be administered over 10 seconds to allow a precise “dose” to be given as a slow bolus. At the same time, the 20 ml syringe will be started as a slow infusion over 5 minutes, using a syringe driver set at 180 ml per hour.

On completion of surgery the obstetrician will be asked to estimate the operative blood loss. Surgical request for a postoperative oxytocin infusion or dose of ergometrine will also be recorded any adverse reactions to these drugs will also be recorded in the same way as reactions to oxytocin.

At forty eight hours post op the patient’s haemoglobin level will be measured, in accordance with routine practice.

The pharmacy department will be responsible for maintenance of trial treatment randomisation codes and there will be 24 hour provision for emergency breaking blind if required clinically.

Ethical issues

The trial will be conducted after a favourable opinion has been received from the Liverpool Paediatric Research Ethics Committee.

The principal ethical issues concern the use of intra-arterial monitoring and randomisation to different rates of oxytocin administration.

From NRES form.

Good Clinical Practice

The Trial will be monitored by the R&D Manager at Liverpool Women's Hospital to ensure the trial conforms to GCP guidelines.

Publication Policy

We aim to publish the completed findings in the British Journal of Anaesthesia, with first author Dr C Mollitt and senior author Dr P Barclay.

Site:

Preoperative assessment clinic and maternity unit, Liverpool Women's Hospital

Number of patients required

36

Power calculation

The Primary Outcome Variable for the trial is difference in Mean Arterial Pressure (MAP) between the two groups.

The null hypothesis is that the mean change in blood pressure after oxytocin administration is identical in each group.

This study uses the same dose and rate of administration as recently work by Thomas et al.[7] found a 19 mm difference between with groups, with a standard deviation of 8.1.

We would consider a difference of 10 mm MAP between groups to be clinically significant.

For a study with a 90% power and a 5% significance level, a sample size of 32 patients (16 per group) is required. Sample sizes were calculated using GraphPad StatMate version 1.01i, GraphPad Software, San Diego California USA, www.graphpad.com, based on the t-test.

Recruitment

Written consent will be obtained from those who wish to participate who fulfil the pre-operative inclusion and exclusion criteria.

Preoperative criteria for patient eligibility -

Inclusion criteria

- All patients who are due to undergo elective Caesarean section under spinal anaesthesia
- ASA grade 1 or 2
- Age > 18

Exclusion criteria

- Conversion to general anaesthesia
- Placenta praevia
- Diabetes Mellitus
- Chronic hypertension
- Patients requiring peri-operative therapeutic anti-coagulant therapy
- Pre-operative anaemia
- Liver disease

- Chronic Renal Failure
- History of anaphylaxis to oxytocin.

Group allocations

Group B will receive active drug via bolus and 0.9% saline via infusion

Group I will receive 0.9% saline via bolus and active drug via infusion

Post-operative assessment on Day 2

Following surgery, Haemoglobin concentration will be measured on Day 2 for all patients, in accordance with usual practice.

Usual Treatment

The patient will continue to take any medication that has been prescribed for them throughout the study period.

Stopping Criteria

The study medication will be discontinued if the patient develops profound hypotension, defined as a decrease in systolic blood pressure of > 40% from baseline, persisting for more than 2 minutes.

Adverse events

All adverse events experienced by the patients will be recorded by the ward staff and reported to the investigators. The adverse events will be reported according to the trust's SAE/AE reporting procedure. Known serious adverse events are listed in the SPC (See attached form, Appendix 1)

Analysis

All results will be collected using a Microsoft Access 2003 database and analysed using GraphPad Prism for Windows v5.01. Haemodynamic variables from each group will be compared using the repeated measures two way ANOVA test.

All data will be analysed on an intention to treat basis.

Financing

The trial will be funded by Research Funds held by Dr Barclay within the Liverpool Women's Hospital R&D Department.

Primary Outcome measure

Maximum change in Mean Arterial Pressure seen in each group after oxytocin administration.

Baseline values are defined as mean arterial pressure values immediately before oxytocin administration.

Secondary Outcome measures

1. Haemodynamic measurement

Change in heart rate

Percentage change in cardiac output

Percentage change in systemic vascular resistance

2. Measures of uterine contractility affecting surgical blood loss

Surgical estimation of uterine tone 10 minutes after the start of infusion

Need for further drugs to contract uterus (oxytocin infusion, ergometrine etc)

EBL in theatre

Fall in Haemoglobin defined as (pre-operative haemoglobin) – (post-operative haemoglobin measured at 48 hrs).

Results

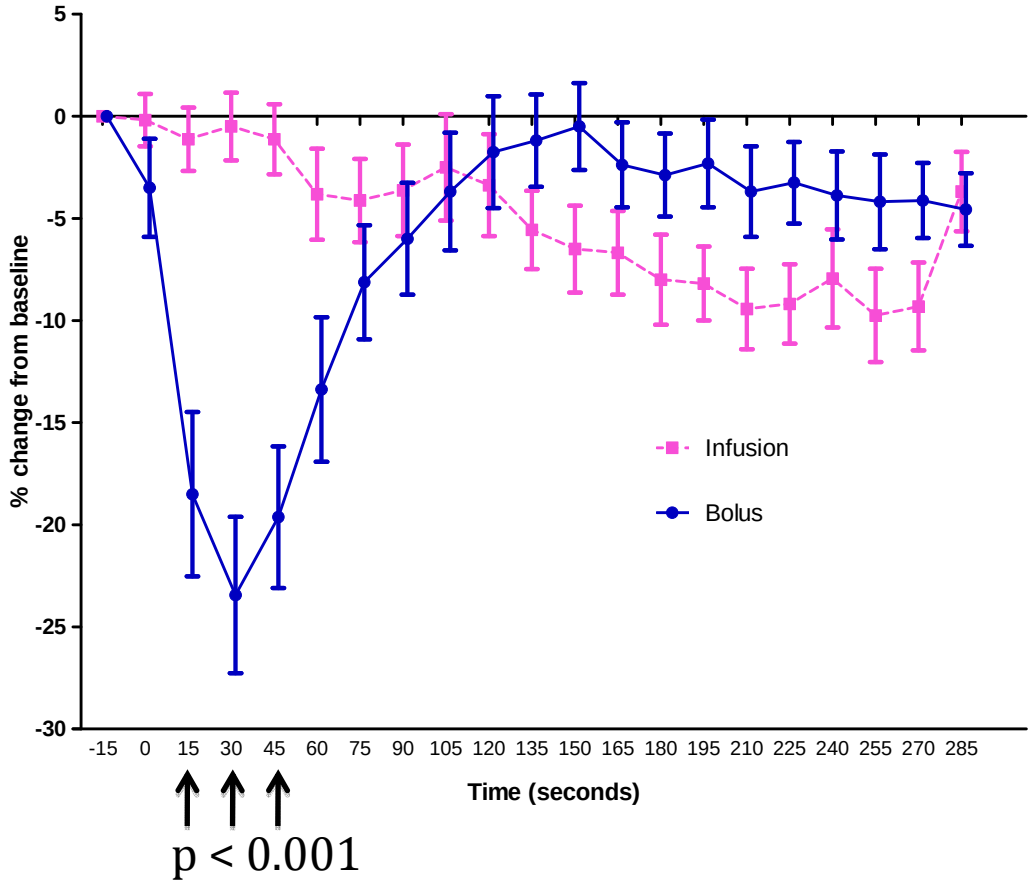
32 patients completed the study, 16 in each group.

Baseline characteristics

The patients had the following baseline characteristics – all values are mean (SD).

	Bolus (n=16)	*Infusion (n=16)*
Age	30.4 (5.6)	31.5 (5.9)
Indications for CS		
- Previous CS	14	12
Breech	0	2
Other	2	2
Parity	1.6 (1.1)	1.6 (0.8)
Baseline MAP	102 (10)	94 (12)
Baseline HR	105 (14)	108 (16)
Ephedrine pre-delivery	5.3 (6.9)	7.5 (8.2)
Ephedrine post delivery	2.4 (3.7)	2.3 (4.3)

Primary outcome: Mean arterial pressure



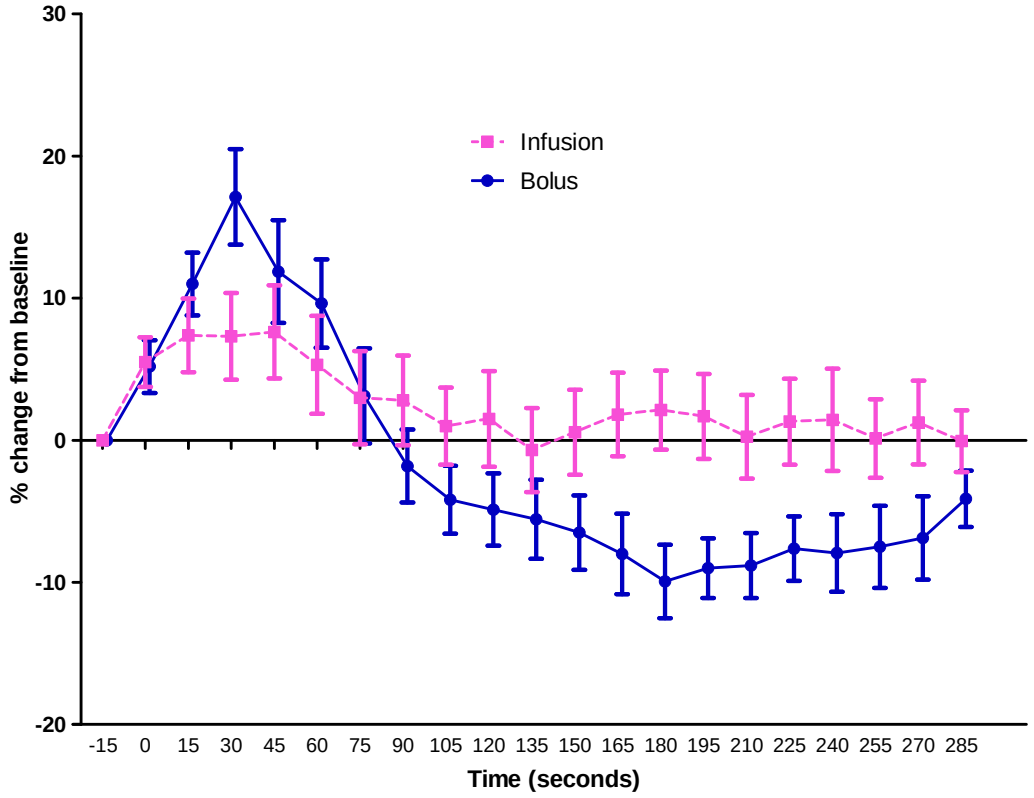
The mean arterial pressure fell by 23% below baseline at 30 seconds in the group of patients who received a bolus of oxytocin. By comparison, the mean fall in blood pressure in the infusion group was 9.4%, which occurred at 210 seconds.

There was a significantly greater fall in MAP in the bolus group than the infusion group at 15, 30 and 45 seconds ($p < 0.001$).

Secondary Outcomes:

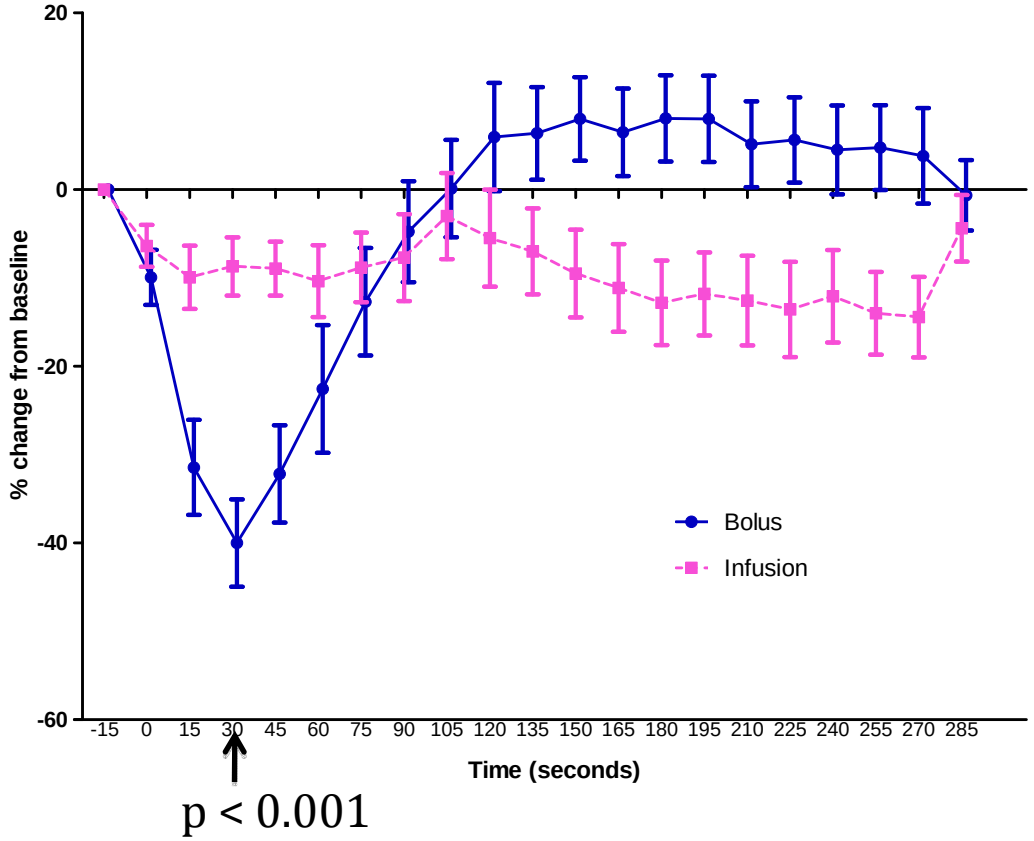
Measures of Haemodynamic stability

Heart rate



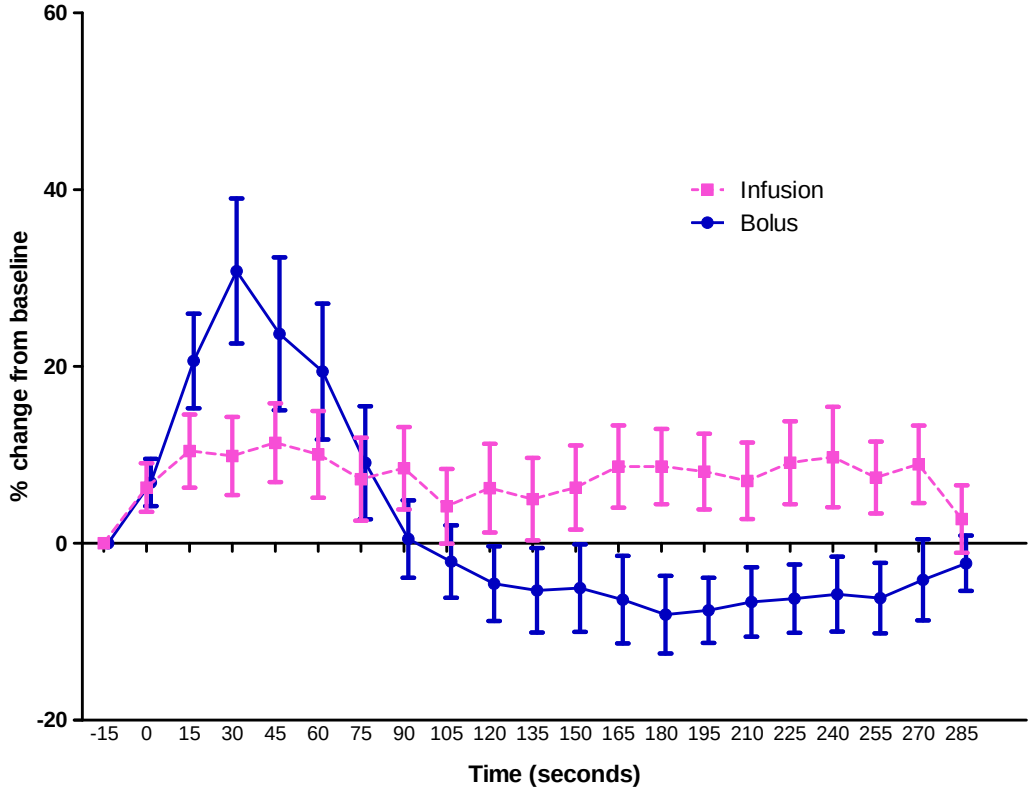
Both groups showed an initial rise in heart rate following administration of oxytocin followed by a rebound fall. There was a significant different in heart rate between the two groups only at 180 seconds.

Systemic vascular resistance



The systemic vascular resistance fell by 40% after administration of oxytocin in the bolus group, with significant difference at 30 seconds between the two groups.

Cardiac output



Patients who received a bolus of oxytocin showed a mean rise in cardiac output of 30%, 30 seconds after injection, which was significantly higher than those in the infusion group ($p<0.05$)

Measures of uterine contractility affecting surgical blood loss

The effects of oxytocin given via bolus and via slow infusion upon uterine contractility were measured using the following parameters. There were no significant differences between the two groups.

	Bolus (n=16)	***Infusion (n=16)***
Estimated blood loss	595 (243)	666 (218)
Uterine tone	7.2 (2.0)	8.1 (1.8)
Postop oxytocin infusion	2	4
Fall in Hb (preop – Day 2 Hb)	1.0 (0.8)	1.2 (0.9)

Discussion

This study has shown that healthy women with good cardiovascular reserve show a significant haemodynamic change following the bolus administration of oxytocin, which is attenuated when the same dose is administered as a slow infusion. Oxytocin by bolus was shown to produce a rapid fall in systemic vascular resistance that peaked at 30 seconds after administration, which required an immediate rise in cardiac output. Despite this compensation, the mean arterial pressure still fell by 23%. When the same dose was given by infusion, the fall in systemic vascular resistance occur far more gradually, peaking at around 210 seconds, which limits the fall in mean arterial pressure to less than 10%.

The fall in mean arterial pressure seen is both statistically and clinically significant. Women with cardiovascular compromise due to hypovolaemia or those with a fixed cardiac output are likely to show a far greater fall in mean arterial pressure in response to a bolus of oxytocin.

There was no difference between the two groups in terms of measures of uterine contractility, which indicated that the 5 unit dose was equally effective when administered over 5 minutes.

Recommendation

Oxytocin should be diluted immediately before administration into a larger volume and should be given slowly over a period 5 minutes to avoid the haemodynamic instability seen with rapid administration.

This should be incorporated into clinical guidelines within Delivery Suite theatres.

Appendix 1:

SPC for Oxytocin (Syntocin®)

Alliance Pharmaceuticals

Avonbridge House
Bath Road
Chippenham
Wiltshire
SN15 2BB

Telephone:	**+44 (0)1249 466 966**
Facsimile:	**+44 (0)1249 466 977**
WWW:	**http://www.alliancepharma.co.uk**
Medical Information e-mail:	**medinfo@alliancepharma.co.uk**

Document last updated on the *e*MC: **Tue 27 March 2007**

Syntocinon Ampoules 10 IU/ml

1. NAME OF THE MEDICINAL PRODUCT

Syntocinon® Ampoules 10 IU/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxytocin PhEur 10 units in 1ml.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

A clear, colourless, sterile solution in 1ml clear glass ampoules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction of labour for medical reasons; stimulation of labour in hypotonic uterine inertia; during caesarean section, following delivery of the child; prevention and treatment of postpartum uterine atony and haemorrhage.

Early stages of pregnancy as a adjunctive therapy for the management

of incomplete, inevitable, or missed abortion.

4.2 Posology and method of administration

Induction or enhancement of labour*:* Oxytocin should not be started for 6 hours following administration of vaginal prostaglandins. Syntocinon should be administered as an iv drip infusion or, preferably, by means of a variable-speed infusion pump. For drip infusion it is recommended that 5 IU of Syntocinon be added to 500ml of a physiological electrolyte solution. For patients in whom infusion of sodium chloride must be avoided, 5% dextrose solution may be used as the diluent (see Section 4.4 "Special warnings and precautions for use"). To ensure even mixing, the bottle or bag must be turned upside down several times before use.

The initial infusion rate should be set at 1 to 4mU/min (2 to 8 drops/min). It may be gradually increased at intervals not shorter than 20 min, until a contraction pattern similar to that of normal labour is established. In pregnancy near term this can often be achieved with an infusion of less than 10mU/min (20 drops/min), and the recommended maximum rate is 20mU/min (40 drops/min). In the unusual event that higher rates are required, as may occur in the management of foetal death *in utero* or for induction of labour at an earlier stage of pregnancy, when the uterus is less sensitive to oxytocin, it is advisable to use a more concentrated Syntocinon solution, e.g., 10 IU in 500ml.

When using a motor-driven infusion pump which delivers smaller volumes than those given by drip infusion, the concentration suitable for infusion within the recommended dosage range must be calculated according to the specifications of the pump.

The frequency, strength, and duration of contractions as well as the foetal heart rate must be carefully monitored throughout the infusion. Once an adequate level of uterine activity is attained, aiming for 3 to 4 contractions every 10 minutes, the infusion rate can often be reduced. In the event of uterine hyperactivity and/or foetal distress, the infusion must be discontinued immediately.

If, in women who are at term or near term, regular contractions are not established after the infusion of a total amount of 5 IU, it is recommended that the attempt to induce labour be ceased; it may be repeated on the following day, starting again from a rate of 1 to 4mU/min (see Section 4.3 "Contra-indications").

Caesarean section*:* 5 IU by slow iv injection immediately after delivery.

Prevention of postpartum uterine haemorrhage*:* The usual dose is 5 IU slowly iv after delivery of the placenta. In women given Syntocinon for induction or enhancement of labour, the infusion should be continued at an increased rate during the third stage of labour and for the next few hours thereafter.

Treatment of postpartum uterine haemorrhage*:* 5 IU slowly iv, followed in severe cases by iv infusion of a solution containing 5 to 20 IU of oxytocin in 500ml of a non-hydrating diluent, run at the rate necessary to control uterine atony.

Incomplete, inevitable, or missed abortion*:* 5 IU slowly iv, if necessary followed by iv infusion at a rate of 20 to 40mU/min or higher.

Children: Not applicable.

Elderly: Not applicable.

Route of administration: Intravenous infusion or intravenous injection.

4.3 Contraindications

Known hypersensitivity to oxytocin or to any of the excipients of Syntocinon. Hypertonic uterine contractions, mechanical obstruction to delivery, foetal distress. Any condition in which, for foetal or maternal reasons, spontaneous labour is inadvisable and/or vaginal delivery is contra-indicated: e.g., significant cephalopelvic disproportion; foetal malpresentation; placenta praevia and vasa praevia; placental abruption; cord presentation or prolapse; overdistension or impaired resistance of the uterus to rupture as in multiple pregnancy; polyhydramnios; grand multiparity and in the presence of a uterine scar resulting from major surgery including classical caesarean section.

Syntocinon should not be used for prolonged periods in patients with oxytocin-resistant uterine inertia, severe pre-eclamptic toxaemia or severe cardiovascular disorders.

4.4 Special warnings and precautions for use

The induction of labour by means of oxytocin should be attempted only when strictly indicated for medical reasons. Administration should only be under hospital conditions and qualified medical supervision. When given for induction and enhancement of labour, Syntocinon must only be administered as an iv infusion and never by iv bolus injection. Administration of oxytocin at excessive doses results in uterine overstimulation which may cause foetal distress, asphyxia and death, or may lead to hypertonicity, titanic contractions or rupture of the uterus. Careful monitoring of foetal heart rate and uterine motility (frequency, strength, and duration of contractions) is essential, so that the dosage may be adjusted to individual response.

When Syntocinon is given for induction or enhancement of labour, particular caution is required in the presence of borderline cephalopelvic disproportion, secondary uterine inertia, mild or moderate degrees of pregnancy-induced hypertension or cardiac disease, and in patients above 35 years of age or with a history of lower-uterine-segment caesarean section.

In rare circumstances, the pharmacological induction of labour using uterotonic agents increases the risk of post patum disseminated intravascular coagulation (DIC). The pharmacological induction itself and not a particular agent is linked to such risk. This risk is increased in particular if the woman has additional risk factors for DIC such as being 35 years of age or over, complications during pregnancy and gestational age more than 40 weeks. In these women, oxytocin or any other alternative drug should be used with care, and the practitioner should be alerted by signs of DIC.

In the case of foetal death *in utero*, and/or in the presence of meconium-stained amniotic fluid, tumultous labour must be avoided, as it may cause amniotic fluid embolism.

Because oxytocin possesses slight antidiuretic activity, its prolonged iv administration at high doses in conjunction with large volumes of fluid, as may be the case in the treatment of inevitable or missed abortion or in the management of postpartum haemorrhage, may cause water

intoxication associated with hyponatraemia. To avoid this rare complication, the following precautions must be observed whenever high doses of oxytocin are administered over a long time: an electrolyte-containing diluent must be used (not dextrose); the volume of infused fluid should be kept low (by infusing oxytocin at a higher concentration than recommended for the induction or enhancement of labour at term); fluid intake by mouth must be restricted; a fluid balance chart should be kept, and serum electrolytes should be measured when electrolyte imbalance is suspected.

When Syntocinon is used for prevention or treatment of uterine haemorrhage, rapid iv injection should be avoided, as it may cause an acute short-lasting drop in blood pressure accompanied with flushing and reflex tachycardia.

4.5 Interaction with other medicinal products and other forms of interaction

Since it has been found that prostaglandins potentiate the effect of oxytocin, it is not recommended that these drugs are used together. If used in sequence, the patient's uterine activity should be carefully monitored.

Some inhalation anaesthetics, e.g., cyclopropane or halothane, may enhance the hypotensive effect of oxytocin and reduce its oxytocic action. Their concurrent use with oxytocin has also been reported to cause cardiac rhythm disturbances.

When given during or after caudal block anaesthesia, oxytocin may potentiate the pressor effect of sympathomimetic vasoconstrictor agents.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with oxytocin. Based on the wide experience with this drug and its chemical structure and pharmacological properties, it is not expected to present a risk of foetal abnormalities when used as indicated.

Oxytocin may be found in small quantities in mother's breast milk. However, oxytocin is not expected to cause harmful effects in the newborn because It passes into the alimentary tract where it undergoes rapid inactivation.

4.7 Effects on ability to drive and use machines

Syntocinon can induce labour, therefore caution should be exercised when driving or operating machines. Women with uterine contractions should not drive or use machines.

4.8 Undesirable effects

As there is a wide variation in uterine sensitivity, uterine spasm may be caused in some instances by what are normally considered to be low doses. When oxytocin is used by iv infusion for the induction or enhancement of labour, administration at too high doses results in

uterine overstimulation which may cause foetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft tissue damage or rupture of the uterus.

Water intoxication associated with maternal and neonatal hyponatraemia has been reported in cases where high doses of oxytocin together with large amounts of electrolyte-free fluid have been administered over a prolonged period of time (see Section 4.4 "Special warnings and precautions for use"). Symptoms of water intoxication include:

1. Headache, anorexia, nausea, vomiting and abdominal pain.

2. Lethargy, drowsiness, unconsciousness and grand-mal type seizures.

3. Low blood electrolyte concentration.

Rapid iv bolus injection of oxytocin at doses amounting to several IU may result in acute short-lasting hypotension accompanied with flushing and reflex tachycardia.

In rare circumstances the pharmacological induction of labour using uterotonic agents increases the risk of postpartum disseminated intravascular coagulation (see section 4.4 Special warnings and special precautions for use).

Oxytocin may occasionally cause nausea, vomiting, haemorrhageor cardiac arrhythmias. In a few cases, skin rashes and anaphylactoid reactions associated with dyspnoea, hypotension, or shock have been reported.

Immune System disorders	
Rare:	Anaphylactoid reaction associated with dyspnoea, hypotension or shock
Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia, bradycardia
Uncommon:	Arrhythmia
Gastrointestinal disorders	
Common:	Nausea, vomiting
Skin and subcutaneous tissue disorders	
Rare:	Rash

4.9 Overdose

The fatal dose of Syntocinon has not been established. Syntocinon is subject to inactivation by proteolytic enzymes of the alimentary tract. Hence it is not absorbed from the intestine and is not likely to have toxic effects when ingested.

The symptoms and consequences of overdosage are those mentioned under Section 4.8 "Undesirable effects". In addition, as a result of uterine overstimulation, placental abruption and/or amniotic fluid embolism have been reported.

Treatment: When signs or symptoms of overdosage occur during continuous iv administration of Syntocinon, the infusion must be discontinued at once and oxygen should be given to the mother. In cases of water intoxication it is essential to restrict fluid intake, promote diuresis, correct electrolyte imbalance, and control convulsions that may eventually occur, by judicious use of diazepam. In the case of coma, a free airway should be maintained with routine measures normally employed in the nursing of the unconscious patient.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The active principle of Syntocinon is a synthetic nonapeptide identical with oxytocin, a hormone released by the posterior lobe of the pituitary. It exerts a stimulatory effect on the smooth musculature of the uterus, particularly towards the end of pregnancy, during labour, after delivery, and in the puerperium, i.e., at times when the number of specific oxytocin receptors in the myometrium is increased.

When given by low-dose iv infusion, Syntocinon elicits rhythmic uterine contractions that are indistinguishable in frequency, force, and duration from those observed during spontaneous labour. At higher infusion dosages, or when given by single injection, the drug is capable of causing sustained uterine contractions.

Being synthetic, Syntocinon does not contain vasopressin, but even in its pure form oxytocin possesses some weak intrinsic vasopressin-like antidiuretic activity.

Another pharmacological effect observed with high doses of oxytocin, particularly when administered by rapid iv bolus injection, consists of a transient direct relaxing effect on vascular smooth muscle, resulting in brief hypotension, flushing and reflex tachycardia.

5.2 Pharmacokinetic properties

The plasma half-life of oxytocin is of the order of five minutes, hence the need for continuous iv infusion. Elimination is via the liver, kidney, functional mammary gland and oxytocinase.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to those already included in other sections of the Summary of

Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate tri-hydrate, acetic acid, chlorobutanol, ethanol and water for injections.

6.2 Incompatibilities

Syntocinon should not be infused via the same apparatus as blood or plasma, because the peptide linkages are rapidly inactivated by oxytocin-inactivating enzymes. Syntocinon is incompatible with solutions containing sodium metabisulphite as a stabiliser.

6.3 Shelf life

Five years

6.4 Special precautions for storage

Store between 2°C and 8°C. May be stored up to 30°C for 3 months, but must then be discarded.

6.5 Nature and contents of container

Clear glass 1ml ampoules. Boxes of 5 ampoules.

6.6 Special precautions for disposal and other handling

Snap ampoules: no file required.

Syntocinon is compatible with the following infusion fluids, but due attention should be paid to the advisability of using electrolyte fluids in individual patients: sodium/potassium chloride (103mmol Na^+ and 51mmol K^+), sodium bicarbonate 1.39%, sodium chloride 0.9%, sodium lactate 1.72%, dextrose 5%, laevulose 20%, macrodex 6%, rheomacrodex 10%, Ringer's solution.

7. MARKETING AUTHORISATION HOLDER

Alliance Pharmaceuticals Ltd

Avonbridge House

Bath Road

Chippenham

Wiltshire

SN15 2BB

8. MARKETING AUTHORISATION NUMBER(S)

PL 16853/0020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 June 1998

10. DATE OF REVISION OF THE TEXT

February 2007

11. Legal Status

POM

SPC for Ephedrine

Date: 17 October 2001 Ephedrine Hydrochloride BP 30mg in 1 ml
PL 1883/6131R

Summary of Product Characteristics

Product Summary

1. Trade name of the medicinal product

Ephedrine Hydrochloride BP 30 mg in 1 ml

2. Qualitative and quantitative composition

Ephedrine Hydrochloride BP 3% w/v.

3. Pharmaceutical form

Injection

Clinical particulars:

4.1 Therapeutic indications

To reduce hypotension during spinal anaesthesia

4.2 Posology and methods of administration

Adults and the elderly
Up to 30 mg in increments of 3 - 7.5 mg.
After the development of hypotension, by slow intravenous administration.
Children
0.5 - 0.75 mg / kg body weight or 17 - 25 mg / M_2 body surface.
After the development of hypotension, by slow intravenous administration.

4.3 Contra-indications

Patients receiving treatment with monoamine oxidase inhibitors (or within 2 weeks of their withdrawal). Coronary thrombosis, diabetes mellitus, ischaemic heart disease, hypotension, thyrotoxicosis, closed angle glaucoma or, in the case of elderly patients prostatic hypertrophy.

4.4 Special warnings and special precautions for use

None stated.

4.5 Interactions with other medicaments and other forms of interaction.

See under 4.3 above.

4.6 Use in pregnancy and lactation

There is no, or inadequate evidence of safety of the drug in human pregnancy, but it has
been in use for many years without apparent ill consequence. If drug therapy during pregnancy is needed the use of this drug is acceptable.

4.7 Effect on the ability to drive or operate machines.

None known.

4.8 Undesirable effects.

The following side effects have been reported:
Giddiness, headache, nausea, vomiting, sweating, thirst, arryhthmias, tachycardia, precordial pain, palpitations, difficulty in micturition, muscular weakness, tremors, anxiety, restlessness and insomnia. In the case of patients with prostatic hypertrophy the retention of urine may become acute.

4.9 Overdose

Symptoms as in 4.8, paranoid psychosis, delusions and hallucinations may occur. Treatment In severe overdosage Diazepam may be required to control CNS stimulation and severe hypertension will require specific therapy.

Pharmacological properties.

5.1 Pharmacodynamic properties

Ephedrine is a sympathomimetic agent with direct and indirect effects on adrenergic receptors. It has alpha and beta- adrenergic activity and has pronounced stimulating

effects on the central nervous system. It causes bronchodilation, relaxes the bladder wall, contracts the sphincter muscles, but relaxes the detruser muscles. It has stimulant
action on the respiratory centre.

5.2 Pharmacokinetic properties

Ephedrine accumulates in the liver, lungs, kidneys, spleen and brain. It is largely excreted unchanged in the urine together with small amounts of metabolites.
It has a plasma half-life reportedly between 3 and 6 hours depending on the urinary pH;
elimination is enhanced and half-life accordingly shorter in acid urine.

5.3 Preclinical safety data

None stated.

6.1 List of excipients.

Water for Injections BP

6.2 Incompatibilities.

Incompatible with anionic salts.

6.3 Shelf life

36 months.

6.4 Special precautions for storage and transport

Do not store above 25°C keep in outer carton

6.5 Nature and contents of containers

1 ml in type 1 colourless neutral glass ampoules. Fusion sealed. Packed into cartons of 10 ampoules.

6. Instructions for use/handling (if applicable)

None applicable

Administrative data

7. Marketing Authorisation Holder.

Macarthys Laboratories Ltd t/a Martindale Pharmaceuticals
Bampton Road, Harold Hill, Romford, RM3 8UG

8. Marketing Authorisation Number.

PL1883/6131R

9. Date of First Authorisation/Renewal of Authorisation.

First authorised: 21st May 1990

10. Date of (Partial) Revision of the Text.

October 2001