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Effect of Oxytocin Bolus Versus Oxytocin Bolus And Infusion On Intraoperative Hemodynamics And Mean Estimated Blood Loss During Caesarean Section.

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I. Introduction

Postpartum haemorrhage (PPH) is the single most important cause of maternal death worldwide, and increases morbidity and mortality in millions of women who give birth. Prophylactic use of uterotonic agents prevents and reduces the morbidity and mortality associated with postpartum haemorrhage. In the developing countries, where the prevalence of anaemia is high, postpartum haemorrhage can have a higher toll on morbidity and mortality and hence the healthcare costs associated with it. According to the World Health Organisation, 25% of maternal deaths occur due to postpartum haemorrhage. In India, the incidence of postpartum haemorrhage is 2-4% following vaginal delivery and 6% following Caesarean section.[1]

In prevention of postpartum haemorrhage, traditional uterotonics (oxytocin or ergot derivatives) outperform prostaglandin analogues because their onset of action is faster and, in the case of oxytocin, there are fewer side effects.[2]

Oxytocin, the most commonly used uterotonic agent, stimulates uterine contractions and is used to prevent and treat postpartum haemorrhage. In moderate doses, oxytocin produces slow, generalized contractions with full relaxation in between; at high doses, it produces sustained tonic contractions.[3]Oxytocin is a nine amino acid peptide produced in the supraoptic and paraventricular nuclei of the hypothalamus. It is stored in the axon terminals in the posterior pituitary as large vesicles. The term oxytocin is derived from the Greek word, oxytocic meaning "quick birth". The uterine contracting property of oxytocin was discovered by the British pharmacologist, Sir Henry Hallett Dale in 1906.

Oxytocin binds to its receptor on the surface of the myometrial cell, interacts with phospholipase C, and generates diacyl glycerol and inositol triphosphate. Diacyl glycerol is involved in the synthesis of prostaglandins, while inositol triphosphate increases calcium concentration in the cell sarcoplasmic reticulum, thereby both play a significant role in the mechanism of myometrial contraction.

Oxytocin, the first polypeptide hormone to be synthesized in 1953 by Vincent Du Vigneau, is the drug of choice for both prevention and treatment of uterine atony after childbirth.[4] According to the recommendations given by the WHO in 2017, oxytocin (i.m./i.v., 10 IU) is recommended as the uterotonic drug of choice in normal labour and Caesarean section. The Guideline Developing Group (GDG) of WHO noted that, in terms of blood loss, there was not enough evidence to recommend oxytocin infusion over IV bolus injection. However, thanks to concerns regarding adverse haemodynamic effects, the GDG considered that if an IV bolus injection is employed, a slow injection rate is preferred and a rapid injection rate should be avoided. The GDG noted that the combination of an oxytocin infusion after an initial IV bolus of oxytocin after Caesarean delivery reduces the necessity for additional uterotonic agents but does not affect the overall occurrence of major obstetric haemorrhage.[5]

According to several reviews on effectiveness and safety of uterotonic drugs in the prevention of postpartum haemorrhage, oxytocin used alone has shown to be effective in reducing the incidence of postpartum haemorrhage.[6-9] However, variable doses of oxytocin bolus and variable rates of its infusion are being used.[10-14]

Hence, we have done this study to compare the efficacy of bolus dose of oxytocin versus bolus with infusion in the control of post-operative blood loss following Caesarean section.

AIM

To compare the efficacy of oxytocin bolus(5U i.v.) with infusion of 20U oxytocin in 20ml over 2 hours versus oxytocin (5U i.v.) with 20ml placebo(normal saline) infusion over 2 hours .

OBJECTIVE

Primary Objective:

- To assess the intraoperative hemodynamics (Heart rate, Mean Blood Pressure)

Secondary outcome:
- Mean estimated blood loss during Caesarean section
- Side effects of oxytocin ,if any

II. Materials And Methods

It is a prospective, randomised, interventional double blinded study done at Sri Ramakrishna Hospital, (*Tertiary Care Hospital*), Coimbatore.

All patients under American Society of Anaesthesiologists I and II above 18 years, scheduled for elective Caesarean section were included in the study.

Patients scheduled for emergency Caesarean section, multiple gestation, placenta previa, patients with significant coagulopathies and with contraindications to regional anaesthesia, history of cardiac, respiratory, renal or hepatic failure, allergy to study medications and those refusing to be involved in the study were excluded.

SAMPLE SIZE

Sample size was determined prospectively using data from previous studies[11] and 75 patients were included in each group.

$$\mathbf{N = [G * z^2 * P * (1–P)]/D^2}$$

Z = alpha risk expressed in z-score	Z = 1.65 (90% alpha risk)
P = 14%=0.14	P = expected prevalence
Q = 1–P	Q = (100-14) =86%=0.86
G = design effect	G = 2
D = 10%=0.1 [i.e. 90% 10%]	D = absolute precision
$N= [2*(1.65)^2*(0.14)*(0.86)]/ (0.1)^2$	N= 66
(Attrition 10% to be added)	

DETAILED DESCRIPTION:

After obtaining institutional ethical committee clearance, written informed consent was taken from all patients. Patients who satisfied the inclusion criteria were allotted to either group by the sealed envelope technique.

Nil per oral guidelines were followed. Patient's blood pressure, heart rate and oxygen saturation were recorded in the pre-operative receiving area.

On shifting to the operating room, patients were co-loaded with a litre of crystalloid. Subarachnoid block with 27G Quincke's spinal needle in the sitting position with bupivacaine Heavy 0.5% 10mg and 20 micrograms of fentanyl was given to achieve a block level of T_6 for the Caesarean section. The patient's heart rate, NIBP, oxygen saturation were recorded every 5minutes during the intra-operative period.

Immediately after delivery of the baby, all patients received a bolus injection of 5U oxytocin over 1 minute followed by an infusion of 20 ml over 2 hrs.

Infusion:

Study group: 20units of oxytocin in 20ml of normal saline

Control group: 20ml normal saline only.

The infusion was prepared by an anaesthesiologist who is not part of the study. Hence the performing anaesthesiologist, patient and the entire operating team were blinded to the group allocation. The infusion was delivered with a syringe pump(TERUMO-terufusion syringe pump 331).

Heart rate (HR), mean blood pressure (MBP) and ECG changes were monitored every minute for the first 5 minutes after delivery and then every 5 minutes throughout the intra-operative period. The monitoring continued in the recovery room till the completion of the infusion.

Any drop in mean blood pressure below 60mmHg was treated with inj. Ephedrine 6mg i.v. bolus and a drop in heart rate below 50/min was treated with inj.Atropine 0.6mg i.v.

The need for further uterotonic agents was at the discretion of the obstetrician. Any patient who required additional uterotonic agents was given inj. Methergine 0.2mg slow i.v. or inj.Carboprost 250mcg i.m. and was excluded from the study.

Post-operative hemoglobin was measured 24 hours after the caesarean section.

STATISTICAL ANALYSIS

The results of this study were analysed using SPSS version 24. The continuous variables were analysed using independent t test and the categorical variables were analysed using chi square test.

III. Results

The groups were comparable in terms of their demographic data. (Table 1)

In figure 1 , the mean blood pressure of the two groups was comparable at all times. There was a fall in blood pressure following spinal anaesthesia and at the first minute following oxytocin bolus in both the groups. But the range of fall was similar in both the groups. This shows that both the groups responded similarly to the bolus dose of oxytocin. The blood pressure was lowest at 20 minutes following delivery in both the groups and there was no statistically significant difference in the blood pressure between the groups during the rest of the observation period.

A similar response was observed with the heart rate as well in figure 2. An increase in heart rate was seen from the second minute following oxytocin bolus which then increased gradually to reach the maximum around the 20^{th} minute. Again the rise in heart rate was comparable between the 2 groups and the difference was not statistically significant.

In the bolus and infusion group(study), the hemoglobin was 10.973gm/dl post-operatively, from a pre-operative value of 11.721gm/dl (table 3). The average hemoglobin in the bolus group(control) was 11.414 pre-operatively and had fallen to 11.008gm /dl in the post-operative period (table 2). This shows that there was a significant drop in hemoglobin levels in both the groups.

Thehemoglobin level in the study group was in the range of 10.9 to 12.7gm/dl and in the control group from 11 to 13gm/dl. On comparing the preoperative and post-operative haemoglobin levels in table 4, there was no significant difference between the 2 groups at either of the times. This reflects that the addition of 20U of oxytocin infusion had no impact on the blood loss as well as the hemodynamics. A single bolus of 5U oxytocin was sufficient to produce adequate uterine contraction in uncomplicated Caesarean sections.

IV. Discussion

Any blood loss more than 500ml with associated hemodynamic instability is considered as post-partum haemorrhage.[15] Controlling and prevention of PPH reduces the morbidity and mortality associated with it. In the Indian population of parturients, there is a high incidence of anaemia.[16] Anaemia with PPH may further worsen the situation, escalate the morbidity and hence the expenditure on healthcare services. Use of uterotonic agents plays a significant role in the control and prevention of postpartum haemorrhage. Several guidelines accept oxytocin as the drug of choice. But the dose and the mode of administration is highly variable in different societies and a consensus is yet to be reached.[17] There is a risk of bleeding with low doses of oxytocin and risk of hemodynamic variation at higher doses.[18] Hence, the risk benefit ratio of each dose should be analysed and the appropriate dose for every ethnic population can be determined. The Royal College Of Obstetricians and Gynaecologists [19] recommend 5 units of intravenous bolus of oxytocin whereas a cochrane database meta-analysis [20] recommends 10 units intravenous bolus for elective uncomplicated Caesarean section. However, the common practice in our country is to give oxytocin as an infusion. Hence we have done this study to determine the effect of bolus dose of oxytocin only versus bolus followed by infusion.

A retrospective mono centric study done by Loytved-Hardegg[21] et al compared the incidence of clinically significant postpartum complications when giving oxytocin 5 U bolus versus 5 U in 100 ml infusion over 5 minutes.1756 patients were included. Their data showed that the group of patients who received the oxytocin infusion had more incidence of manual removal of placenta. They concluded that oxytocin when given as an infusion was not sufficient to produce adequate uterine contraction and hence separation of placenta. These patients required manual removal of the placenta.

Oxytocin is secreted in a pulsatile manner, with the frequency of secretion increasing during labour and reaching a maximum during the second stage of labour.[22]This supports the fact that oxytocin works better when given as a bolus. Higher efficacy of oxytocin bolus is due to high plasma concentration flooding the receptors. Its short half-life and the longer time needed to attain a steady state further move the balance in favour of bolus doses. Also a continuous infusion of oxytocin is associated with receptor desensitisation.[23]This reflects the attenuation in hemodynamic changes that occurs after the second dose of oxytocin.

In a study by Bhattacharya et al [24] that included 80 patients, the hemodynamic effect of 3units of oxytocin bolus over 15 seconds was compared with 3 units of oxytocin infusion over 15 minutes. They observed that, though the uterotonic action was comparable between the groups, a significant fall in mean arterial pressure (MAP) and increase in heart rate was noted in the bolus group. However, in our study, we have noticed that there was no significant fall in MBP or increase in HR when 5 units of oxytocin was given over a minute as a bolus.

J S Thomas et al [25] compared the hemodynamic effects of oxytocin 5 units when given as a bolus versus as infusion over 5 minutes in women undergoing Caesarean section. The bolus group had a significant fall in MBP and increase in the heart rate. However, there was no difference in estimated blood loss. We had not observed any significant fall in hemodynamics with the 5 units bolus dose of oxytocin and the further addition of the infusion didn't make a significant difference in the estimated blood loss between the groups. In our study, both the study and control groups had received 5 units oxytocin bolus. It was noted that when the bolus was given over a minute, there was no significant hemodynamic variation.

This shows that controlled injection of oxytocin over a minute prevents hemodynamic variation and can be considered a safe option in all patients. The additional 20 units' infusion over 2 hours had no effect on the hemodynamics and blood loss. The drop in hemoglobin in the two groups was comparable. Hence we may conclude that a bolus dose of 5 units of oxytocin given over a minute provides adequate uterine contraction without any significant hemodynamic variation and blood loss.

V. Conclusion

Thus, we conclude that a single bolus dose of 5U of oxytocin given intravenously over a minute produces good uterine contraction without any adverse hemodynamic variation and without exaggerated blood loss.

FIGURE 1

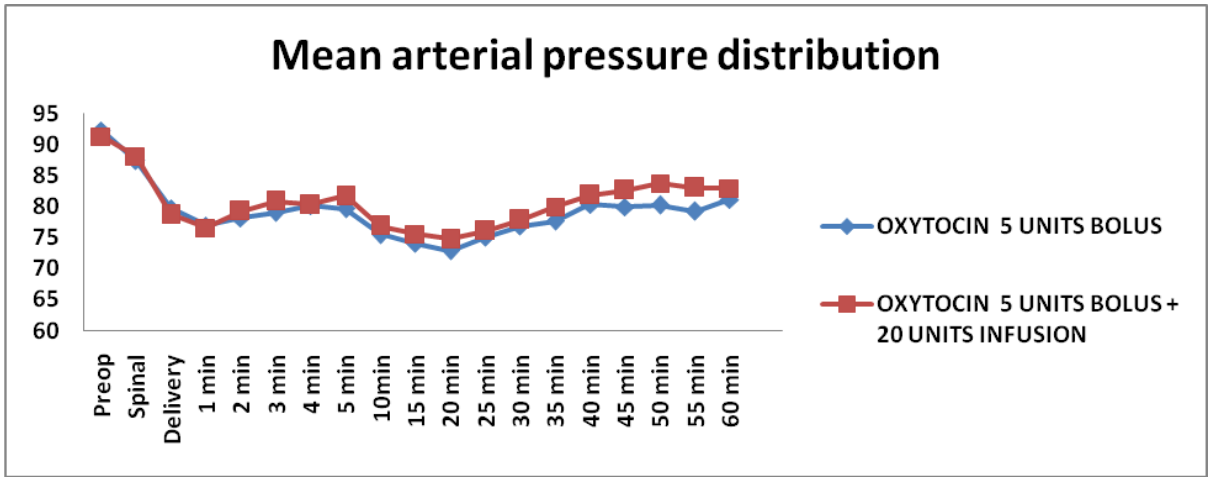

FIGURE 2

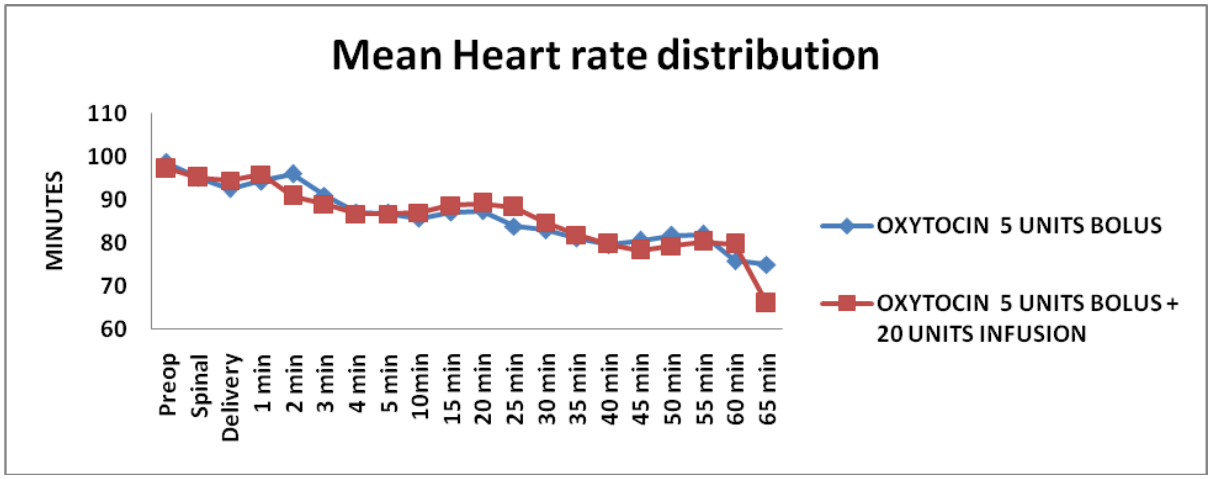

FIGURE 3

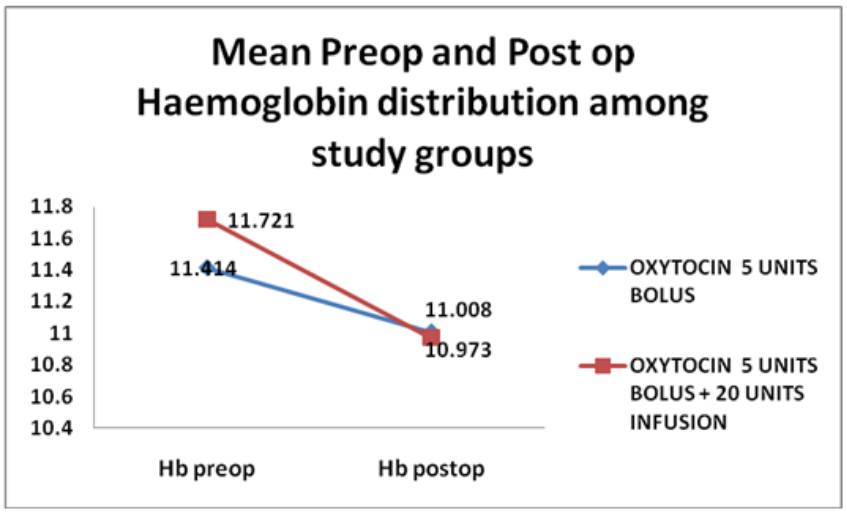

TABLE 1

GROUP	N	Mean Age	Std. Deviation	P value
OXYTOCIN 5 UNITS BOLUS (CONTROL)	75	29.50	5.042	.588
OXYTOCIN 5 UNITS BOLUS + 20UNITS INFUSION (STUDY)	75	29.08	3.563	

TABLE 2

		N	Mean	Std. Deviation	P value
OXYTOCIN 5 NITS BOLUS (CONTROL)	**Hb preop**	75	11.414	1.1326	.000*
	Hb postop	75	11.008	1.2931	

TABLE 3

		N	Mean	Std. Deviation	P value
OXYTOCIN 5 UNITS BOLUS + 20 UNITS INFUSION (STUDY)	**Hb preop**	75	11.721	1.0147	.000*
	Hb postop	75	10.973	.9785	

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