A randomized trial of pulsatile vs continuous oxytocin infusion for labor induction

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Summary

In a prospective randomized study, 560 pregnant women were subjected to labor induction with continuous or pulsed intravenous oxytocin infusion. There were no significant differences with respect to maternal history, Bishop score and perinatal morbidity. The mean induction to delivery interval was shorter in the pulsed infusion group than in the continuous infusion group (325±63 vs 433±67 min in primiparous, $p<0.001$ and 204±52 vs 236±87 min in multiparous women, $p<0.01$). The mean amount of oxytocin administered in the pulsed infusion group was also significantly lower than in the continuous infusion group (4.7±0.6 mU/min versus 9.6±3.4 mU/min in primiparous, $p<0.001$ and 2.1±0.4 mU/min versus 5.2±2.3 mU/min in multiparous women, $p<0.001$). Our study demonstrates that pulsatile administration of oxytocin is as safe as continuous intravenous infusion, requires less oxytocin and is more effective as it reduces labor duration.

Key words: Oxytocin; Pulsatile; Oxytocin infusion; Perinatal morbidity.

Introduction

Oxytocin is widely used for labor induction or augmentation under careful monitoring for uterine overstimulation. Several authors have reported the efficacy of oxytocin infusion with dose increments at 30-minute intervals for labor induction [1]. Despite the guidelines of ACOG [2], many centers continue the use of older oxytocin infusion protocols, with dose increments at less than 30-minute intervals [3, 4, 5]. However recent clinical studies agree that prolonged intervals of 30-40 or even 60 minutes are superior to shorter dosage intervals in terms of safety and efficacy [5].

Unjustified use of oxytocin may cause serious side-effects, as uterine overstimulation, uterine rupture, fetal hypoxia, neonatal jaundice and water intoxication. It is of great importance that oxytocin should be used with caution, at the lowest possible dose and with accuracy, in order to produce satisfactory progress in labor.

It is known that endogenous oxytocin is released in a pulsatile manner. Pavlou *et al* [6] first described a protocol of pulsatile oxytocin infusion. It has been proved that pulsatile oxytocin infusion is a more effective way of oxytocin use, since it produces better results in labor induction and reduces the total dose required. It is probable that pulsatile infusion is more consistent to the physiology of endogenous oxytocin release in vivo [7].

The purpose of our prospective randomized study was to compare the efficacy and safety of pulsed oxytocin infusion with the traditional continuous intravenous infusion for labor induction.

Materials and Methods

A total of 560 parturients were studied at the University Clinic, Areteion Hospital. All were admitted for labor induction with intact membranes and were randomized to one of the two induction protocols described below, after written informed consent. Our inclusion criteria were: gestational age 37 weeks or more, cephalic presentation and one of the following indications for labor induction: mild pregnancy-induced hypertension, gestational diabetes, postdatism, oligohydramnios and intrauterine growth retardation. No prostaglandin preparations were used for cervical ripening. Oxytocin was not used prior to the patient entry to the study. Vaginal digital examination was performed for determination of cervical dilatation and Bishop score before randomization. Women with placenta previa, previous myomectomy, twin gestation, hydramnios, active genital herpes, estimated fetal weight over 4,500 g and hypertension requiring magnesium sulfate administration were excluded from the study. A total of 270 patients were randomized in the continuous oxytocin infusion group (group A). The infusion was performed through a simple intravenous apparatus. The initial oxytocin dose was 2 mU/min and was gradually increased in dose increments of 2 mU/min at 30-minute intervals until adequate uterine activity was produced. A total of 290 patients were randomized to group B, receiving pulsatile oxytocin infusion through an electronic infusion pump (Infusomat Secura, Brown Melsungen, A.G.). Oxytocin infusion started with 2 mU/min and was doubled every 15 minutes, and titrated to allow no more than 7 contractions every 15 minutes. A 1000-ml Dextrose 5% in water solution with 20 IU of synthetic oxytocin was used in both protocols. All patients were monitored by external cardiotocography for at least 20 minutes prior to oxytocin administration. Amniotomy was performed when clinically indicated (head station no higher than -2 and cervical dilatation over 2 cm). In case of uterine hyperstimulation, defined as five or more contractions in 10 minutes with duration over 90 seconds or a baseline uterine tone of 25 mmHg, oxytocin was discontinued.

Our data were analyzed using the unpaired t-test for continuous data and the Fisher exact t-test or χ^2 test for non-continuous data, as required.

Results

A total of 560 patients were included in the study, with 270 assigned to the continuous-infusion-protocol (group A) and 290 to the pulsatile infusion protocol (group B). The patients in both groups were similar concerning

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obstetrical history, age, parity and gestational age (Table 1). The most common indication for labor induction in both groups was post-term pregnancy.

There was to difference in the mean bishop score at the time of induction of labor (5.3±2.1 vs 5.5±2.3) (Table 2). There was also no difference in the patients with stained meconium between the two groups.

The length of labor was statistically significantly lower in primiparous (325±63 min) as well in multiparous women (204±52 min) who were subjected to labor induction with pulsed intravenous oxytocin infusion compared to those who received continuous oxytocin infusion (433±67 min for primiparous and 236±87 min for multiparous).

The average dose of oxytocin administered per minute was significantly lower in primiparous (4.7±0.6 mU/min) and multiparous women (3.1±0.4 mU/min) subjected to labor induction with pulsative compared to those with continuous oxytocin infusion.

Furthermore, the mean uterine activity integral units were similar (1710±279 and 1812±329) between the two groups. In 16 patients (5.5%) of the group subjected to pulsatile oxytocin infusion and in 29 patients (10.7%) of the group subjected to continuous oxytocin infusion, it was necessary to reduce the oxytocin dose because of uterine hyperstimulation. The difference was statistically significant ($p<0.05$).

Table 3 presents the mode of delivery and newborn status according to the method of the induction of labor. There was no statistical difference in the rate of normal delivery. There was also no statistical difference in the rate of cesarean section between the two groups (22.9% vs 20%). Induction failure was responsible for one cesarean section in group A patients; 26 sections were performed due to dystocia and 35 due to fetal distress. The most common indication for cesarean section in group B was secondary arrest of dilatation or descent, while fetal distress occurred in 20 cases, and induction failure was responsible for one case.

Neonatal status assessed by 5-min Apgar Score and umbilical vein pH were similar in both groups. Finally the mean birth weight of the newborns was similar in both groups (3296±588 g vs 3375±576 g).

Table 1. — *Demographic and clinical information of the patients.*

	Group A (n=270)	Group B (n=290)	P
Maternal age (yrs, mean±SD)	24.2±3.9	23.7±3.7	NS
Primiparous	155 (57.4%)	164 (56.5%)	NS
Multiparous	115 (42.6%)	126 (43.5%)	NS
Gestational age (wks, mean±SD)	40.4±0.25	40.5±0.25	NS
Postdates	196 (72.6)	215 (74.2)	NS
Mild pregnancy-induced hypertension	28 (10.3%)	33 (11.4%)	NS
Gestational diabetes	24 (8.9%)	25 (8.6%)	NS
Oligohydramnios	2 (0.7%)	2 (0.7%)	NS
Intrauterine growth retardation	20 (7.5%)	15 (5.2%)	NS

Group A = continuous infusion group.
Group B = pulsatile infusion group.

Table 2. — *Clinical and labor characteristics of the two groups.*

	Group A (n=270)	Group B (n=290)	P
Bishop score at onset of induction (mean±SD)	5.3±2.1	5.5±2.3	NS
Mean interval from induction to delivery in prim. (min)	433±67	325±63	0.001
Mean interval from induction to delivery in mult. (min)	236±87	204±52	0.01
Meconium stained (n%)	32 (11.8%)	29 (10%)	NS
Average intravenous oxytocin dose in prim. (mU/min)	9.6±3.4	4.7±0.6	0.001
Average intravenous oxytocin dose in mult. (mU/min)	5.2±23	3.1±0.4	0.001
Mean Kpa S/15 min	1710±279	1812±329	NS
Reduction in dose in oxytocin needed	29 (10.7%)	16 (5.5%)	0.05

Table 3. — *Mode of delivery and newborn status in patients with labor induction with pulsatile or continuous oxytocin administration.*

	Group A (n=270)	Group B (n=290)	P
Normal delivery	208 (77.1%)	232 (80%)	NS
Cesarean section	62 (22.9%)	58 (20%)	NS
Mean Apgar Score (5 min)	8.2±0.2	8.3±0.4	NS
Mean umbilical vein pH	7.22±0.06	7.24±0.07	NS
Mean birth weight (g)	3,296±588	3,375±576	NS

Discussion

In 1906 Dale demonstrated that myometrial tissue would contract when exposed to posterior pituitary extracts in vitro. By 1913 Watson had begun to use such extracts for the induction of labor [8].

Complications such as uterine rupture and its attendant morbidity and mortality discouraged this practice until Theobald described the administration of oxytocin in intravenous drip in 1948 [9]. In 1949 De Vigneaud demonstrated the structure of the octapeptide oxytocin, work for which he was later awarded the Nobel Prize in Chemistry [10].

Oxytocin is secreted episodically in spurts or pulses during pregnancy and labor. Specific receptors for oxytocin are present in the uterine smooth muscle and the occupied receptors become temporarily unavailable to the infused or circulating oxytocin for binding. The duration of the oxytocin-receptor binding or receptor occupation is not known [11]. Pulsatile administration of oxytocin mimics episodic release of oxytocin during labor and thus continuous flooding of the uterus and saturation of unavailable or occupied receptor sites can be avoided.

The concentration of oxytocin administered, the rate of infusion and the interval between dose increments are subjects of study and debate. Some investigators suggest low-dose protocols (2-5 U/l) and others prefer the high dose protocols, (10 U/l) [12, 13]. The proposed infusion rate in recent studies is 0.5-1.0 mU/min, instead of the usual dose of 3.0 mU/min. [14]. According to recent reports, the proposed intervals for oxytocin dose increments ranged between 15-60 minutes, without significant differences in labor duration [15].

Some authors suggest that expanding the time interval between dose increments is a safer and just as effective method of induction [16]. Our purpose was to verify whether we could obtain adequate contractions sooner by raising the dose increments and using longer intervals between increments. In particular, we studied whether we could decrease the number of inductions or decrease the total delivery time by getting to a higher oxytocin level sooner than that in the ACOG protocol [17]. By doubling the infusion rate in the pulsatile group, we have apparently demonstrated a method of reaching effective uterine activity in a shorter time than in the traditional protocols.

Muller *et al.* [15] have demonstrated that oxytocin infusion rates for labor induction can be safely increased by relatively high increments, provided that adequate time is allowed for the establishment of maximal contractility. Fuchs *et al.* [18] have shown that plasma oxytocin levels in patients receiving up to 3 mU/min, are not significantly different from levels before labor induction. In their study, plasma levels corresponding to women during spontaneous labor were not reached until infusion rates reached 4-6 mU/min and were increased linearly in relation to time and infusion rate.

Many authors suggest that the average dose of oxytocin administered per minute as well as the total dose of oxytocin were significantly lower in the pulsed women [7, 13, 19, 20].

Our data confirm that patients in the pulsatile protocol not only required lower amounts of oxytocin, but also a significant decrease in time from induction to delivery was seen. The last observation is in disagreement with other authors who have suggested that the average induction to delivery interval was similar with pulsed or continuous oxytocin administration [12, 14].

According to our results the frequency of failed induction was similar between the pulsatile and the continuous group. This observation is in agreement with other investigators [14].

Many authors suggest that induction of labor with pulsatile oxytocin was not associated with increased uterine activity [15]. According to our results the opposite observation was noted. A significantly higher incidence of uterine hyperstimulation was found in women who underwent induction of labor with continuous intravenous oxytocin infusion.

We believe, as do many other authors, that the method of pulsatile oxytocin administration leads to less receptor saturation and more physiologic response of the uterus to oxytocin stimulation [7].

The newborn status, as indicated by the 5-min Apgar Score and umbilical vein pH, was not different between our groups. Thus, as many authors have suggested, pulsatile infusion of oxytocin is as efficacious as continuous infusion concerning the mode of delivery as well as the perinatal morbidity [15, 20].

We conclude that pulsatile administration of oxytocin is as effective as continuous infusion. However, the rate of uterine hyperstimulation, the time from induction to delivery, and the amount of oxytocin administration are lower when the method of the pulsatile oxytocin infusion for induction of labor is used.

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