A randomised clinical trial to determine the effect of beta-adrenergic blocking with propranolol on labour

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Background. Dysfunctional labour is a common problem, particularly in disadvantaged communities. Women who are anxious during labour have high adrenaline levels, which could lead to dysfunctional uterine contractions through beta-adrenergic receptor stimulation.

Objective. To determine whether beta-adrenergic blocking with propranolol would reduce the incidence of dysfunctional labour and decrease the caesarean section rate at Universitas and Pelonomi hospitals, Bloemfontein, South Africa.

Study design. A double-blind randomised controlled trial.

Methods. Women with prolonged labour during the active phase were randomised into receiving propranolol or a placebo. A standard protocol for managing labour was maintained, including pain relief and oxytocin infusion when necessary. Age, gravidity, parity, maternal weight, blood pressure and pulse rate before and 1 hour after administration of propranolol or placebo, amount of oxytocin given before and after randomisation, time and method of pain relief, time and method of delivery, Apgar score, fetal weight, indication for caesarean section, and any complications experienced were documented.

Results. Of the 53 women enrolled in the study, 25 received propranolol and 28 the placebo. There was no statistically significant difference between the two groups in number of caesarean sections performed (p=0.59). The only statistically significant difference was the number of cases in which oxytocin augmentation was used after randomisation. In the propranolol group, only 7 (28.0%) received oxytocin after propranolol was given, while in the placebo group 17 (60.7%) received oxytocin after the placebo was administered (p=0.03).

Conclusion. Beta-adrenergic blocking with propranolol did not reduce the caesarean section rate or the duration of labour in our population, but decreased the need for oxytocin.

S Afr J OG 2013;19(2):53-55. DOI:10.7196/SAJOG.643

Dysfunctional labour is a common problem, particularly in disadvantaged communities. In South Africa it is one of the major factors leading to prolonged labour and caesarean sections. Oxytocin is often used in these patients, many of whom are primigravidas. The safety of oxytocin has been questioned owing to its adverse effects, usually preceded by overstimulation of uterine contractions. Cibils *et al.* demonstrated in 1962 that adrenaline relaxes the human uterus at term.[1] In contrast, noradrenaline commonly produces an increase in uterine activity in humans, in terms of both resting tone and frequency of contractions.[2] Increased tone and frequency of contractions are believed to result from stimulation of alpha-receptors, and reduced activity from stimulation of beta-receptors. In the rhesus monkey, labour is suppressed by the discharge of adrenaline when the animal is threatened. Women who are anxious during labour and have high adrenaline levels, which stimulate the beta-receptors, may experience dysfunctional labour. Epidural analgesia has been shown to lower adrenaline levels, and its use in women with dysfunctional labour has been recommended. Unfortunately there are risks involved in its administration, and a certain level of competence is required from the practitioner.

Adamson *et al.* reported a 50% reduction in the caesarean section rate among nulliparous patients treated with 2 mg propranolol every 4 hours, without an increase in neonatal or maternal morbidity.[3] Earlier, Sanchez-Ramos *et al.* showed in a randomised trial that low-dose administration of propranolol in patients with dysfunctional labour augmented with oxytocin safely reduced the need for caesarean section, particularly among patients with inadequate uterine contractions.[4]

Material and methods

The study was conducted over a 12-month period at Universitas and Pelonomi hospitals, Bloemfontein, South Africa, and a convenience sample size was used. The study population consisted of women in the active phase of labour with cervical dilatation of less than 2 cm per 2-hour period. Exclusion criteria included previous caesarean section, any signs of obstructed labour, presentation other than vertex,

Table 1. Differences in variables during labour between the propranolol and placebo groups

Factor	Group		*p*-value*
	Propranolol (*N*=25)	Placebo (*N*=28)	
Median time to delivery (min)	210	218	0.68
Caesarean sections, *n* (%)	13 (52.0)	11 (40.7)	0.59
Indications for caesarean section, *n* (%)			0.75
Poor progression	8/13 (61.5)	7/11 (63.6)	
Obstructed labour	5/13 (38.5)	4/11 (36.4)	
Mean 5-minute Apgar score	8.92	8.96	0.89
Oxytocin given before randomisation, *n* (%)	5 (20.0)	10 (35.7)	0.33
Oxytocin given after randomisation, *n* (%)	7 (28.0)	17 (60.7)	0.03

*$p<0.05$ was considered significant.

maternal cardiomyopathy, diabetes mellitus, multiple pregnancies, vaginal bleeding, systolic blood pressure of less than 100 mmHg, and asthma. After giving informed consent, subjects were assigned to receive either propranolol or placebo according to a computer-generated randomisation list. Each hospital had its own randomisation list with consecutively numbered and sealed envelopes containing the questionnaire form and medication. The patients and the doctors managing their labour were blind to the assignment information. Subjects were given either propranolol 2 mg or a matching placebo after randomisation. Only one dose of propranolol or placebo was given. A standard protocol for managing labour in the two hospitals was maintained, including pain relief and oxytocin infusion when necessary. Oxytocin was instituted at 2 mU per minute and doubled every 15 minutes until at least three contractions were noted in a 10-minute period. The maximum dose of oxytocin was 32 mU/min. The following information was documented on the questionnaire form: envelope number, age, gravidity, parity, maternal weight, blood pressure and pulse before and 1 hour after the propranolol or placebo was given, quantity of oxytocin given before and after randomisation, time and method of pain relief, time and method of delivery, Apgar score, fetal weight, indication for caesarean section, and any complications experienced. A duplicate partogram was included as part of the questionnaire. Routine observations during labour included blood pressure, pulse, temperature, contractions and fetal heart rate. Continuous electronic fetal heart rate monitoring was done in all subjects. Caesarean section was performed for poor progression of labour, obstructed labour, or fetal distress.

Approval for the study was obtained from the Ethics Committee of the Faculty of Health Sciences, University of the Free State.

Results

Age, parity, maternal weight, fetal weight and mean amount of pethidine administered were similar in the propranolol and placebo groups.

Of the 53 women enrolled in the study, 25 received propranolol and 28 the placebo. None of the women who were enrolled and randomised were excluded from the study. The median time from when the medication was given until delivery was 210 minutes in the propranolol group and 218 minutes in the placebo group, which was not statistically significant (p=0.68). None of the women experienced an excessive decrease in blood pressure or pulse rate.

Thirteen women in the propranolol group (52.0%) and 11 in the placebo group (40.7%) had a caesarean section. This difference was not statistically significant (p=0.59). No caesarean section was done for fetal distress in either of the groups. In the propranolol group, 8 caesarean sections (61.5%) were done for poor progression and 5 (38.5%) for obstructed labour. In the placebo group, 7 caesarean sections (63.6%) were done for poor progression and 4 (36.4%) for obstructed labour. Again the difference was not statistically significant (p=0.75). Mean Apgar scores at 5 minutes were 8.92 in the propranolol group and 8.96 in the placebo group (p=0.89).

Oxytocin was used in 5 women (20.0%) in the propranolol group before randomisation, compared with 10 (35.7%) in the placebo group (p=0.33). The only statistically significant difference between the two groups in this study was the number of cases in which oxytocin was needed after randomisation. Only 2 additional women needed oxytocin after receiving propranolol, whereas an additional 7 needed it after receiving the placebo. In total, 7 women (28.0%) received oxytocin after propranolol was administered, while 17 (60.7%) received oxytocin after the placebo (p=0.03). Table 1 summarises these variables, showing the differences between the two groups.

Discussion

Adamson *et al.*[3] found that administration of propranolol in labour reduced the caesarean section rate in nulliparous women. Although the numbers in our study were small, we did not observe a tendency towards a reduction in the caesarean rate. There were, however, fewer patients who needed oxytocin after receiving propranolol than after placebo. This may have been influenced by the fact that more women in the placebo group received oxytocin before randomisation. It is possible that propranolol had the same effect on uterine activity as oxytocin, but with a different mechanism. Stressful situations such as labour can cause an increase in serum catecholamines, which could bind to the beta-2-receptors to cause relaxation of the uterine muscle. By blocking these receptors with propranolol, uterine activity may be increased. Garcia and Garcia presented evidence of raised plasma levels of catecholamines in women with abnormal labour.[5]

The differences in outcome between our study and that of Adamson *et al.*[3] could be explained by the different populations. Most of our subjects were black Africans, who tend to have

android pelvises with an increased incidence of cephalopelvic disproportion. Some of the women in the propranolol group (20.0%) developed obstructed labour after administration of the propranolol. As mentioned above, obstructed labour was one of the exclusion criteria for the study, but it is possible that subtle signs of cephalopelvic disproportion were missed at the time of inclusion of these patients into the study – most of our subjects gave birth at Pelonomi Hospital, where doctors are often less experienced. Another explanation for the difference in outcome could be that Adamson *et al.*'s study was limited to nulliparous women,[3] whereas we included multiparous women too.

The use of propranolol in labour seems to be safe, as shown by very similar 5-minute Apgar scores in the two groups, as well as the fact that no caesarean section was done for fetal distress. Although propranolol did result in an increase in uterine activity, as demonstrated by the reduction in oxytocin use, no reduction in the caesarean section rate was observed in our study population.

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