GYNAECOLOGIA ET PERINATOLOGIA

Gynaecol Perinatol Vol 26, No 3–4; 119–148 Zagreb, July–December 2017

IZVORNI ČLANAK
ORIGINAL PAPER

Gynaecol Perinatol 2017;26(3–4):119–123

Department of Obstetrics and Gynaecology, University Clinical Hospital Center Zagreb

IMPACT OF INTRAVENOUS OXYTOCIN ON LUNG HAEMODYNAMICS AND GAS EXCHANGE DURING CAESAREAN SECTION UNDER GENERAL AND SPINAL ANAESTHESIA

Kresimir Reiner, Josip Juras, Marko Čačić, Slobodan Mihaljević

Original scientific paper

Keywords: oxytocin, Caesarean section, lung haemodynamics, gas exchange

Summary. Numerous studies have proven haemodynamic effects of oxytocin, yet there is not much knowledge about the impact of oxytocin on lung haemodynamics and gas exchange. Our goal was to determine the potential impact of intravenous oxytocin on lung haemodynamics and arterial oxygen saturation in patients undergoing Caesarean delivery and to determine the possible difference in arterial oxygen saturation between general and spinal anaesthesia after intravenous administration of oxytocin. *Methods.* Total of 215 patients scheduled for elective Caesarean delivery were included in the study and randomised into two groups: Caesarean section under spinal anaesthesia and Caesarean section under general anaesthesia. After excluding the patients with severe intraoperative blood loss and those given the standard doses of oxytocin, 70 patients (35 per group) were left for statistical analysis. Patients in both groups were given 10 international units (IU) of oxytocin as a bolus dose plus 10 IU of oxytocin in infusion through 3 minutes, after clamping and cutting of the umbilical cord. Oxygen saturation values throughout the whole procedure were compared between the two groups. *Results.* Oxygen saturation values decreased more often and to a greater degree in general anaesthesia group than in the spinal anaesthesia group after intravenous administration of oxytocin (all $P < 0.05$). *Conclusion.* Drop in arterial oxygen saturation after intravenous oxytocin is inside the safety range among full-term healthy partiurents undergoing spinal or general anaesthesia for Caesarean section. Larger studies on patients with risk factors are needed to conclude the safety of oxytocin in those patients.

Introduction

Intravenous administration of oxytocin after Caesarean section delivery and umbilical cord transaction is a common and widely accepted method for reducing postpartum bleeding and prevention of uterine atony. There are numerous clinical studies which have proven that after intravenous administration of oxytocin, due to the vasodilation effect, reducement in peripheral resistance occurs and MAP (mean arterial pressure) decreases. In response to those changes, compensatory tachycardia occurs and stroke volume of the heart increases.[1–3] Although the impact of oxytocin on systemic circulation is known for decades, there is not much knowledge about the impact of oxytocin on lung hemodynamic and gas exchange. Due to our clinical observations, we decided to examine the impact of oxytocin on arterial oxygen saturation in caesarean section patients and to determine the possible difference in arterial oxygen saturation between general and spinal anaesthesia after intravenous administration of oxytocin.

Methods

Ethical approval for this study (Ethical Committee N° 021-1/63-2015) was provided by the Ethical Committee of the Department of Obstetrics and Gynaecology of the University Clinical Hospital Centre Zagreb, Zagreb, Croatia on 7 May 2015. We started recruiting the patients from whom the written informed consent was obtained. The trial was publically registered at the Australian New Zealand Clinical Trials Registry (trial ID: ACTRN12616000166471). All of the patients were scheduled for elective Caesarean section and randomised to the anesthetic technique into two groups: Caesarean section under spinal anaesthesia and Caesarean section under general anaesthesia. Patients with underlying lung disease (asthma, obstructive lung disease) were not included in the study because of the possible impact of impaired gas exchange on oxygen saturation, as well as the patients with hypertension and preeclampsia due to the possible intraoperative haemodynamic instability and subsequent impact on the lung haemody-

namics and oxygen saturation. All of the patients were monitored by the standard monitoring methods: pulse oxymeter placed on the second finger of the right hand, non-invasive blood pressure cuff placed on the left hand and electrocardiogram (ECG) electrodes, second lead. Values of arterial oxygen saturation, pulse and MAP before spinal and general anaesthesia induction were taken as the baseline values, and then were registered every 5 minutes until the end of the surgery. Patients undergoing general anaesthesia were preoxyganted with oxygen via the face mask for 3 minutes. For general anaesthesia induction, patients were given 5 mg/kg of thiopental and 1.5 mg/kg of succinylcholine. For general anaesthesia maintenance, a combination of 50% oxygen/N2O and 1% sevoflurane was used. Patients were mechanically ventilated with 8 mL/kg of ideal body mass tidal volume and respiratory frequency between 10–15 breaths/min. Positive end-expiratory pressure (PEEP) of 4 hPa was also applied. 10 mg bolus doses of rocuronium were applied intravenously for muscle relaxation maintenance and 150–250 μg of fentanyl were randomly given intravenously for analgesia after the umbilical cord transection. In the spinal anaesthesia group, patients were given 1.9–2.2 mL of 0.5% hyperbaric levobupivacaine + 20 μg of fentanyl in the L3–L4 interspace. To test the adequacy of the spinal block, pin prick test was used to ensure the block height reached the T4 level. Patients were receiving oxygen via the nasal catheter during the whole operating procedure and hypotension was treated by bolus doses of 10 mg of efedrine. Patients with estimated intraoperative blood loss of more than 800 mL were excluded from the study, considering blood loss could impact pulse oxymeter readings. We also excluded from the study those patients receiving standard doses of oxytocin intraoperatively: 5 IU as a bolus dose plus 5 IU in infusion through 3 minutes. We decided to include only those patients who received 10 IU of oxytocin as a bolus dose plus 10 IU in infusion through 3 minutes, after clamping and cutting of the umbilical cord. The mentioned doses of oxytocin were given on the request of obstetrician, due to the obviously clinically low uterine tone and subsequent need for higher doses of oxytocin. Time

Table 1. The general data of patients

Variable	General anaesthesia	Spinal anaesthesia	Z	P
Age (years)	34 (28–37)	32 (28–35,8)	0,905	0,365
Parity	2 (1–2,8)	2 (1–2)	1,426	0,154
Body mass index (kg/m^2)	29,41 (26,7–34,4)	27,4 (25,7–30,6)	1,639	0,101
Operation time (min.)	38 (31,2–42,8)	45 (39,3–52)	2,979	0,003

Z – Mann-Whitney U test value; P – probability

Table 2. Oxygen saturation differences between the two groups during whole procedure

Time of saturation measurement	Type of anaesthesia	Median	25th percentile	75th percentile	Z	P
Preoperative	General	100.00	99.00	100.00	–2.275	0.023
	Spinal	99.00	98.00	100.00		
5 minutes	General	100.00	99.00	100.00	–0.491	0.624
	Spinal	100.00	98.00	100.00		
10 minutes	General	99.00	98.00	100.00	–2.085	0.037
	Spinal	100.00	99.00	100.00		
15 minutes	General	99.00	96.00	99.00	–3.615	<0.001
	Spinal	100.00	99.00	100.00		
20 minutes	General	98.00	96.00	99.00	–3.119	0.002
	Spinal	100.00	98,00	100.00		
25 minutes	General	98.00	96.00	99.00	–2.468	0.014
	Spinal	99.00	98.00	100.00		
30 minutes	General	98.00	95.00	99.00	–2.549	0.011
	Spinal	99.00	98.00	100.00		
35 minutes	General	97.50	93.00	99.00	–3.043	0.002
	Spinal	99.00	98.00	100.00		
40 minutes	General	96.50	94.50	99.00	–2.882	0.004
	Spinal	99.00	98.00	100.00		
45 minutes	General	96.00	94.50	98.00	–2.246	0.025
	Spinal	99.00	97.00	100.00		
50 minutes	General	96.00	95.50	96.50	–2.792	0.005
	Spinal	99.00	98.00	100.00		
55 minutes	General	97.00	97.00	97.00	–1.451	0.147
	Spinal	99.00	98.50	99.50		
60 minutes	General	.	.	.		
	Spinal	99.00	99.00	99.00		

Z – Mann-Whitney U test value; P – probability

of the intravenous administration of oxytocin was recorded. Any decrease in arterial oxygen saturation below the baseline value after intravenous administration of oxytocin was recorded. Oxygen saturation values were compared between the two groups.

Considering the difference in oxygen saturation of 2% around 10 minutes after its administration (spinal group SD ±2, general anaesthesia group ±3; α=0,05; β=90%) a samle size of 35 per group was calculated. Numerical data were described by the mean value (arithmetic mean) and standard deviation in the case of normal distributions. In other cases, data were described by the median and the interquartile range. The normality of distribution of numerical variables was tested by the Shapiro-Wilk test. Independent sample t-test was used to explore the difference of normally distributed numerical variables and Mann-Whitney U test to explore the difference in the cases of deviation from normal distribution. Level of significance was set to *P*=0.05. Data was statistically analysed by the program MedCalc Statistical Software version 13.1.2 (MedCalc Software bvba, Ostend, Belgija; http://www.medcalc.org; 2014).

Results

Date of start of enrolment of patients was 3 August 2015. Total of 215 patients were included in the study. After excluding the patients with intraoperative blood loss of more than 800 mL and/or patients receiving standard doses of oxytocin, we managed to collect 70 patients (35 per group) for statistical analysis. No differences concerning the age, parity and body mass index (BMI) were found between the two groups of patients *(Table 1)*, as well as the preoperative values of oxygen saturation *(Table 2)*. Time needed for the onset of spinal anaesthesia (around 7 minutes) explains longer duration of Caesarean delivery in the spinal anaesthesia group, as well as the later application of oxytocin and the time of the first drop in oxygen saturation among the spinal anaesthesia patients *(Table 3)*. After administration of oxytocin, oxygen values decreased more often in general anaesthesia group than in the spinal anaesthesia group *(Table 2)* and also to a greater degree in general anaesthesia group than in the spinal anaesthesia group *(Table 3)*. We observed no haemodynamic instability among both groups of patients during the whole procedure *(Table 4)*, as well as no pathological ECG findings or symptoms of impaired cardiac activity.

Table 3. Differences in oxytocin application time and oxygen saturation values between two groups

	Type of anaesthesia	Median (interquartile range)	Z	P
Oxytocin administration start minute	General	10 (8–12)	–4.427	<0.001
	Spinal	14 (10–17)		
Minute of decrease in oxygen saturation after administration of oxytocin	General	3 (0–4)	–2.353	0.019
	Spinal	5 (3–12)		
Difference between preoperative saturation and lowest one after administration of oxytocin (%)	General	3 (2–5)	–2.558	0.011
	Spinal	1 (1–3)		

Z – Mann-Whitney U test value; P – probability

Table 4. Mean arterial pressure values differences between two groups of patients during the whole procedure

Preoperative	general	99.00	95.00	111.00	–1.299	0.194
	spinal	97.00	92.00	108.00		
5 minutes	general	109.00	98.00	124.00	–5.451	<0.001
	spinal	75.00	62.00	91.00		
10 minutes	general	100.00	87.00	116.00	–4.306	<0.001
	spinal	82.00	61.00	92.00		
15 minutes	general	92.00	81.00	103.00	–2.374	0.018
	spinal	85,00	76,00	92,00		
20 minutes	general	86.00	78.00	102.00	–2.757	0.006
	spinal	80.00	72.00	85.00		
25 minutes	general	87.50	75.00	99.00	–2.955	0.003
	spinal	75.00	70.00	81.00		
30 minutes	general	89.00	77.00	106.00	–4.377	<0.001
	spinal	72.00	68.00	77.00		
35 minutes	general	88.50	81.50	103.00	–4.475	<0.001
	spinal	70.00	64.00	80.00		
40 minutes	general	92.50	83.00	102.00	–3.517	<0.001
	spinal	73.00	68.00	81.00		
45 minutes	general	103.50	96.00	109.00	–3.296	0.001
	spinal	75.00	72.00	79.00		
50 minutes	general	101.50	91.50	105.00	–2.027	0.043
	spinal	78.00	74.00	86.00		
55 minutes	general	99.00	99.00	99.00	–0.707	0.480
	spinal	83.50	77.00	103.00		
60 minutes	general	.	.	.		
	spinal	122.00	122.00	122.00		

Z – Mann-Whitney U test value; P – probability

Discussion

In 1999, Thibonnier and colleagues conducted in vitro experiments on endothelial cells from human umbilical vein, aorta and pulmonary artery. They concluded that human vascular endothelial cells express oxytocin receptors that are structurally identical to the uterine and mammary oxytocin receptors and that via these receptors, oxytocin produces a calcium-dependent vasodilatory response via stimulation of the nitric oxide pathway.[4] Due to its vasodilation effect on pulmonary blood vessels, oxytocin could theoretically increase right to left pulmonary shunting, which would result in impaired gas exchange and consequently lower arterial oxygen saturation. Regarding the results of our study, this could explain the drop in oxygen saturation among the both groups of patients after intravenous administration of oxytocin *(Figure 1)*. However, there was a statistically significant higher occurence of oxygen saturation drop among the general anaesthesia patients as well as the greater degree of drop in oxygen saturation

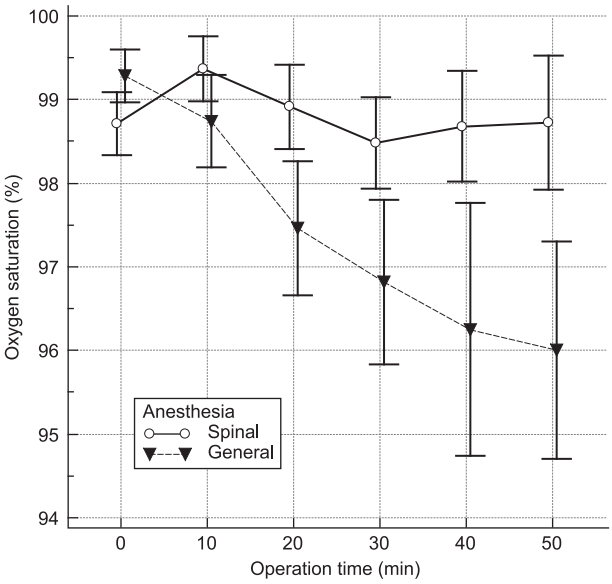

Figure 1. Oxygen saturation through out the whole procedure by the type of anesthesia

Throught the procedure, drop in arterial oxygen saturation is greater among the general anaesthesia patients compared with the spinal anaesthesia group

among the general anaesthesia patients. Pulmonary gas exchange is regularly impaired during general anaesthesia with mechanical ventilation due to atelectasis formation, which lead to increased right to left pulmonary shunting and consequently lower arterial oxygen saturation. In addition to formation of atelectasis, intermittent closure of airways during mechanical ventilation reduces the ventilation of dependent lung regions which may become regions with a low ventilation/perfusion ratio.[5,6] Also, functional residual capacity is significantly decreased among all full-term pregnant patients who additionally predispose those patients to lower arterial oxygen saturation.[7] It is to conclude that all of the factors mentioned above predispose patients undergoing general anaesthesia for Caesarean section to lower oxygen saturation values compared to patients undergoing spinal anaesthesia. Consequently, it is not surprising that the drop in oxygen saturation, after intravenous administration of oxytocine, was more frequent and more profound among the general anaesthesia patients compared with patients undergoing spinal anaesthesia, despite using preoxygenation and PEEP to prevent such changes. It is very important to observe that the drop in oxygen saturation appears to be constant among the general anaesthesia patients *(Table 2, Figure 1)*. It remains a question if the drop in oxygen saturation is due solely to the effects of mechanical ventilation or it is the consequence of combined effect of mechanical ventilation and intravenous oxytocin. However, median lowest value of oxygen saturation after administration of oxytocine was 3%[2–5] among general anaesthesia patients which is considered to be inside the safety range, concerning the median preoperative oxygen saturation value of 100% among that group of patients. Median lowest value of oxygen saturation among spinal anaesthesia patients was 1%[1–3] which is also inside the safety range (median preoperative oxygen saturation value among spinal anaesthesia patients was 99%). It is to conclude that the higher dosage of oxytocin than recommended, as well as the mode of delivery we used in our study (10 IU as a bolus dose plus 10 IU in infusion through 3 minutes) are safe concerning arterial oxygenation. However, it is important to highlight that our research was done among healthy full-term parturient with no risk factors which could additionally alter arterial oxygen saturation (ie. asthma, preeclampsia, obesity). It is also to mention that the lung haemodynamics and gas exchange are very complex processes which can be influenced by various factors. In our study, we used peripheral oxygen saturation measured via the pulse oxymeter as a surrogate marker for gas exchange. However, pulmonary gas exchange can be very well described using non-invasive pulse oxymeter readings, if compared with more invasive solutions such as arterial oxygen partial pressure measurement.[8] According to available literature, no larger studies were done concerning the potential problem in arterial oxygenation following intravenous oxytocin in patients with risk factors undergoing Caesarean section. There is only a case report published in 2013. on acute hypoxemia in a parturient with primary ciliary dyskinesia following the administration of intravenous oxytocin.[9] As already mentioned in the results, we observed no haemodynamic instability or pathological ECG changes among both groups after administration of oxytocin.

10 IU of oxytocin given as a bolus dose, plus additional 10 IU of oxytocin in infusion through 3 minutes are safe concerning arterial oxygenation among full-term healthy partiurents with no severe intraoperative blood loss (more than 800 mL), undergoing spinal or general anaesthesia for Caesarean section. However, larger studies on patients with risk factors (ie., lung disease, obesity) are needed to conclude the safety of oxytocin in those patients.

References

1. Langesaeter E, Rosseland LA, Stubhaug A. Haemodynamic effects of repeated doses of oxytocin during Caesarean delivery in healthy parturients. British Journal of Anaesthesia 2009;103:260–2.

2. Thomas JS, Koh SH, Cooper GM. Haemodynamic effects of oxytocin given as i.v. bolus or infusion on women undergoing Caesarean sectio. British Journal of Anaesthesia 2006;98:116–19.

3. Weis FR Jr, Markello R, Mo B et al. Cardiovascular effects of oxytocin. Obstetrics and Gynecology 1975;46(2):211–4.

4. Thibonnier M, Conarty DM, Preston JA, et al. Human vascular endothelial cells express oxytocin receptors. Endocrinology 1999;140(3):1301–9.

5. Hedenstierna G, Rothen HU. Atelectasis formation during anesthesia: causes and measures to prevent it. Journal of Clinical Monitoring and Computing 2000;16(5–6):329–35.

6. Hedenstierna G. Airway closure, atelectasis and gas exchange during anaesthesia. Minerva Anestesiologica 2002;68: 332–6.

7. Nørregaard O, Schultz P, Ostergaard A et al. Lung function and postural changes during pregnancy. Respiratory Medicine 1989;83(6):467–70.

8. Kjaergaard S, Rees S, Malczynski J et al. Non-invasive estimation of shunt and ventilation-perfusion mismatch. Intensive Care Med 2003;29(5):727–34.

9. Nandhakumar A, Silverman GL. Acute hypoxemia in a parturient with primary ciliary dyskinesia following the administration of intravenous oxytocin: a case report. Canadian Journal of Anesthesia 2013;60(12):1218–21.

Corresponding address: Kresimir Reiner: University Clinical Hospital Center Zagreb, Department of Obstetrics and Gynecology, Petrova 13, Zagreb 10000, Croatia; *e-mail:* kresimirovichmd@gmail.com

Paper received: November, 12, 2018., accepted: December, 28, 2018.

UTJECAJ INTRAVENSKOG DAVANJA OKSITOCINA NA HEMODINAMIKU I IZMJENU PLINOVA TIJEKOM CARSKOG REZA KOD OPĆE I SPINALNE ANESTEZIJE

Kresimir Reiner, Josip Juras, Marko Čačić, Slobodan Mihaljević

Izvorni znanstveni članak

Ključne riječi: oksitocin, carski rez, plućna hemodinamika, izmjena plinova

Sažetak. Premda su brojne studije dokazale hemodinamske učinke oksitocina, u literaturi nema podataka o učinku oksitocina na plućnu hemodinamiku i izmjenu plinova. Cilj ove studije jest pokazati učinak intravenskog oksitocina na plućnu hemodinamiku i saturaiju arterijske krvi kisikom u pacijentica za carski rez te utvrditi postoji li razlika u saturaciji arterijske krvi kiskom između opće i spinalne anestezije nakon intravenske primjene oksitocina. *Ispitanici i metode.* 215 pacijentica za elektivni carski rez je uključeno u studiju. Pacijentice su randomizirane u dvije skupine s obzirom na tip anestezije: spinalna ili opća anestezija. Nakon isključivanja pacijentica s povećanim intravaskularnim gubitkom volumena te pacijentica koje su primile standardne doze oksitocina, 70 pacijentica (35 po skupini) je ostalo za statističku analizu. Pacijentice u obje skupine su primile 10 IJ oksitocina intravenski u bolusu te 10 IJ oksitocina infuziji kroz 3 minute nakon klemanja pupkovine. Vrijednosti saturacije krvi kisikom su bilježene tijekom cijelog operativnog zahvata te su uspoređene između obje skupine. *Rezultati.* Saturacija arterijske krvi kisikom je opadala značajno češće te u većoj mjeri u skupini pacijentica koje su primile općU anesteziju za carski rez. ($P < 0,05$). *Zaključci.* Pad saturacije kisikom u arterijskoj krvi je unutar sigurnosnog ranga kod zdravih pacijentica u terminu tijekom carskog reza u općoj ili spinalnoj anesteziji. Potrebne su dodatne studije u pacijentica sa rizičnim faktorima kako bi se utvrdila sigurnost oksitocina u tih pacijentica.