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Chest Pain Secondary to Use of Oxytocin in Obstetric Patients at Transanesthesic

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Abstract:

Background and objectives *- Chest pain is related with the use of oxytocin administration for bleeding control during caesarean or birth. The objective of this study is to evaluate the incidence of chest pain with the use of oxytocin during caesarean operation.*

Methods *- Prospective study of one-cohort including 415 obstetric patients in who was administered oxytocin during caesarean operation. Previous chest pain and use of oxytocin were identified, as anesthesia type and technique used in each case. Clinical and sociodemographic data were identified and reported. Cero point was settled at admission time, the presence of chest pain was considered as outcome event. Clinical data like blood pressure, heart rate, oxygen saturation, electrocardiographic (EKG) anomalies, chest pain, flushing and restlessness were evaluated at 1, 3, 5, 10, 15 and 20 minutes from administration. Long Rank test was used to probe hypothesis, and Kaplan Maier curve for outcome measure.*

Results *- 415 women of 26.5 + 8.5 years were included, 88% receive urgent caesarean operation and in 22% labor was induced. Oxytocin bolus of 5 Units (U) were administered in 110 patients (26.5%). Infusion doses was from 10 to 25 U. Chest pain was present in 83(20%) (p=0.005), tachycardia in 152(36.62%)(p=0.001), hypotension in 81(19.5%)(p=0.702), flushing in 55(13.25%)(p=0.185), discomfort in 212(51.08%)(p=0.019), EKG changes in 4(0.96%)(p=0.001) and others in 4 cases (0.96%). Log Rank = 0.014.*

Conclusions *- Oxytocin administration is not harmless and must be used carefully, because high and constant doses increase the secondary cardiovascular effects significantly.*

Keywords *- Chest pain, Oxytocin, Obstetric patients, caesarean.*

Introduction

Oxytocin bolus dose during cesarean operation could be significantly reduced if uterine contraction still effective. Modifications in clinical practice about this could reduce the adverse cardiovascular effects of high bolus doses of oxytocin, but placenta extraction techniques would need modification.[1]

In obstetric practice the use of oxytocin is very common as uterotonic for induction and conduction of birth work, and constitutes the elective drug to promote uterine contraction after birth or caesarean operation.[2]

Doses for oxytocin infusion are not well determined and in some cases use to be empiric, with doses between 5, 10, 15, 20 and 30 Units (U) for intravenous infusion at 120/ml/h after umbilical ligation.[3,4]

Some studies recommend the use of 10,15 or 20 U of oxytocin in 40ml of solution to administration in 20 minutes, as an alternative to the infusion of 30 U in 500cc of solution for a period of 4 hours after the initial bolus.[4,5]

Oxytocin administered in bolus could predispose tachycardia and hypotension directly related with dose, and

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this could be lethal in some cases of previously cardiovascular compromised patients.[6,7]

Ischemia signs like chest pain, dyspnea and ST segment enlargement, ST segment depression, and T wave inversion could appear and have been directly related with oxytocin dose and administration speed.[7]

The best was of oxytocin administration after delivery or caesarean operation is not well established, it had bee estimated an effective doses 90% (ED90) of oxytocin in healthy women during caesarean in 0.35 U. The same group analyzed 30 women who require caesarean operation and more than 2 hours of oxytocin stimulation during delivery, and found a ED90 of 3 U.[3,4]

The purpose of this study is to know the presence of precordial pain secondary to the use of oxytocin in obstetric patients.

Methods

This was a prospective, descriptive, analytical and longitudinal study performed in 415 obstetric patients who receive caesarean operation under regional anesthesia, and oxytocin was administered after delivery, in the General Regional Hospital #17, Cancún, Quintana Roo.

Sample size was calculated from prognostic studies studying the outcomes of oxytocin administration during caesarean after obtain the product, using Wald test after a Cox regression model was applied for one or more factors, with a relative risk of 2. According to the revision of indexed scientific journals the proportion of exposed patients with chest pain after oxytocin administration is 30%, with a confidence level (1-alpha) of 95%, and statistical power of 90%.

Using statistical package EPPI-INFO the minimum sample size was calculated in 376 patients, with a loss adjustment of 15%: 432 subjects are required for this study.

Patients were randomized according to a previously excel generated table until complete the calculated sample size with patients who meet inclusion criteria (Appendage 1).

Inclusion Criteria. Patient with caesarean operation under regional anesthesia. Use of intravenous oxytocin. Patients over 18 years old. Exclusion Criteria. Patients with caesarean intervention under general anesthesia. Patients under 18 years old. Patient who don't want to be included. Patient who don't speak Spanish. Patients with some mental dysfunction. *Elimination criteria* Change of anesthetic technique. Patient with more than one uterotonic administered. Ketamine use during procedure.

Statistical analysis- Chest pain incidence, unusual weakness and discomfort after oxytocin administration during caesarean operation was asked directly to patients during surgery and registered with a numerical value. Arterial pressure, heart rate and oxygen saturation were register too. T student test for independent samples and Chi square for nominal variables was used to compare sociodemographic variables (age, weight, height) and clinical variables (arterial pressure, heart rate, oxygen saturation, discomfort, chest pain, flushing and electrocardiographic changes). Construction of a logistic regression model was performed to determine the independent variable. Model variables with a value of p = 0.1 was entered to remove spurious associations, and determine hazard ratio. Kaplan Maier model was performed to determine the survival outcome with chest pain, and likewise log-rank. Statistical significance was considered with a p = 0.05. Results are presented in the corresponding tables.

Table 1

Variables	***μ***	**±**	***Min-max***
Years (Years)	18	8.5	18-38
Weight (Kilograms)	70.33	25.5	41-125
Size (Meters)	1.52	0.12	1.41-1.62
		No.	%
Caesarean	Elective	50	12.4
	Urgency	365	87.9
Anaesthesia	Peridural Block	297	71.5
	Subarachnoid Block	55	13.2
	Mixed block	63	15.1
Previous use of Oxytocin	Inductoconduction	92	22.1
	Without inductoconduction	323	77.8
Use of adyuvants	Midazolam	149	35.9
	Fentanyl	122	29.39

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Oxytocin dose during inductoconduction	5-10U	Average time of inductoconduction	6.5hr
		No	%
Trans-anesthesic bolus of oxytocin		110	26.5
Transanesthesic infusion of oxytocin (U)	10U	44	10.6
	15U	22	5.3
	20U	344	83.9
	25U	5	1.2
Infusion duration (Minutes)	49		
Dilution volume (ml)	535.2		

Table 2: Comparison of cases with oxytocin bolus application with and without inductoconducción

N=415

Inductoconduction	*Transanesthesic oxytocin bolus*	*Total number*	*Chest pain(n)*	*Censured*	
				Number	*%*
No	*Without oxy bolus*	*247*	*49*	*198*	*80.2*
	With oxy bolus	*92*	*14*	*78*	*84.8*
	Global	*339*	*63*	*276*	*81.4*
Yes	*Without oxy bolus*	*61*	*13*	*48*	*78.7*
	With oxy bolus	*15*	*15*	*0*	*0.0*
	Global	*76*	*28*	*48*	*63.2*
Global	*Global*	*415*	*91*	*324*	*78.1*

Survival rate, with chest pain outcome secondary to oxytocin exposure in inductoconduction or bolus.
N= Total of patients, n=chest pain events % = porportion of events.

Table 3: Independent sample proof for INFUSION group and INFUSION+BOLUS group

		95 % Confidence Interval	
	p	INFERIOR	SUPERIOR
Chest pain incidence	.005	-0.021	0.160
Tachycardia incidence	.000	-0.186	-0.001
Hypotension incidence	.702	-0.076	0.093
Flushing incidence	.185	-0.062	0.130
		-0.065	0.132
Discomfort	.019	0.031	0.248
EKG changes	.000	-0.071	-0.000

Origin: p< 0.05= Statistically significative difference.

Table 4: Log Rank Test.

	Chi ²	**gl**	***P* value**
Log Rank (Mantel-Cox)	***6.015***	**1**	**.014**

Origin: Equality test survival distributions for different levels of the transanesthesic Oxytocin bolus.
ₐ: adjusted for inductoconduction.
This table exemplified the oxytocin exposure in inductoconduction or bolus associated with chest pain in the first 15 minutes, and confirms the alternative hypothesis with a log Rank of p=0.014.

Results

For the present study 451 patients were included and 21 were excluded (8 for insufficient data collection, 13 underwent general anesthesia) and 15 eliminated for carbetocin or ergometrine, with a final sample of 415 patients.

Demographic characteristics are presented in Table 1. The median age was 26.5 + 8.5 years old; with a median weight of 70.33 kg + 25.5 kg and a median height of 1.52 m. + 0.12 m.

For the presentation 365 (87.9%) were performed as urgent caesarean and 50(12.4%) patients receive elective caesarean. Epidural block was the preferred anesthetic procedure in

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297(71.5%), 55 (13.2%) receive subarachnoid block and 63(15.1%) a mixed technique.

In the management of oxytocin 92(22.1%) patients receive inductoconduction and 323(77.8%) without it. Inductoconduction was performed with oxytocin 5-10 U for about 6.5 hours. Other adjuvants were registered as follows: 149(35.9%) patients receive 0.5 a 4.5mg IV, 122(29.39%) use fentanyl 50-250mcg IV. Ketamine was not used. During trans-anesthetic period a bolus of oxytocin 5 U was administered in 110 patients, 26.5% of population. Oxytocin infusion was between 10 to 25 U with the next distribution: 5 patients received 25 U (1.2 %), 344(83.9 %) patients received 20 U, 22 patients received 15 U (5.3 %), and finally 44 patients received 10 U (10.6 %). All the previous doses with an average infusion period of 49 minutes and dilution of 535.2 ml.

Primary outcomes to evaluate include chest pain, tachycardia, hypotension, discomfort, flushing and others, with registry at 1,3,5,10,15 and 20 minutes after oxytocin administration.

Chest pain: 83 patients present this symptom (20 %), founding association with the use of oxytocin between 1-5 minutes [p=.005, CI (95%) = 0.202- 0.160] (Tables 2, 3).

Tachycardia was present in 152 (36.62%) patients associated with infusion rate and oxytocin dose, with higher incidence between 3-5 minutes [p= 0.000, CI (95%) = 0.186- 0.001]

Hypotension was present in 81 (19.5 %) patients founding association between oxytocin dose and infusion rate, and higher incidence between 3 to 5 minutes [p= 0.702, CI (95%) = -0.076- 0.934].

Flushing was present in 55 (13.25%) patients It was a higher incidence in minute 3 after oxytocin administration [p= 0.185, CI (95%) = -0.062-0.130]

Discomfort was present in 212 (51.08 %) patients and the higher incidence was between3-10 minutes [p= 0.019 CI (95 %)= 0.031 -0.248]. Electrocardiographic changes were registered in 4 (0.96%) patients after oxytocin infusion with ST depression (Fig. 9), [p= 0.000 CI (95%) = -0.071--0.000] (Other effects were nausea and dizziness in 4 (0.96 %) patients.

The patients with 5 U oxytocin bolus administrations were compared to patients without this dose. It was a significative difference in the incidence of tachycardia, chest pain and discomfort (Table 3), with 14 cases in patients with previous inductoconduction and bolus, and 15 cases in patients without inductoconduction. 49 patients present these symptoms without inductoconduction or bolus oxytocin dose and 13 patients with inductoconduction and without bolus dose.

To realize an hypothesis test the long Rank test was applied for possible outcomes and found that the group that receive oxytocin in bolus and infusion present chest pain for short time, principally between 5-15 minutes (p=0.0005)(Table 4).

Discussion

Incidence of adverse effects after oxytocin administration were as follows:

Chest pain in 83 patients (20%), with significative association between oxytocin administration between 1-5 minutes [p=0.005, CI (95%) = 0.202- 0.160].

Release of uterine renin could predispose coronary arteries spasm, explaining the myocardial ischemia in pregnant woman during caesarean operation and have been related with the vasoespastic effect of the tocolythic agents like amines, oxytocin, ergonovine, terbutaline, aminophyline, epinephrine and carbetocin.[7-12]

Cardiovascular effects of oxytocin have been poor described in pharmacological books, but could be clinically significative in vulnerable patients.[13-17]

Results of this study including chest pain and other cardiovascular effects like tachycardia, flushing, hypotension, electrocardiographic changes and discomfort are similar to the ones reported since 2008 and 2010, by Svasnstro et. al. and Lohit et. al. respectively.[11,14]

Oxytocin administered in bolus could produce dose dependent tachycardia and hypotension, and this could be significative and in some cases lethal.[13] Myocardial ischemic signs could be present as chest pain, dyspnea and ST segment enlargement, ST segment depression and T wave abnormalities.[11,14,15]

In the present study the incidence of chest pain increase between 1-10 minutes after the administration of 5U of oxytocin in bolus and the subsequent continuous infusion at 0.002 U/ml/min (Fig. 12), corresponding to 52.38% of total cases registering chest pain between 1-20 minutes after administration, coinciding with previous studies in Australia and New Zeland.[18]

Clinical practice guidelines of United Kingdom, Canada and Australia recommend a bolus of 5 U of oxytocin slowly. Although this, the dose is associated with significative secondary effects like hypotension and other cardiovascular effects and for this reason it is suggested that 2 U in bolus could be a safe dose for healthy patients.[11,15,17,19] These results are supported by the present study.

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Chest pain presented in patients with infusion of oxytocin at 0.0048-0.0095 U/ml/min, between 15 to 20 minutes, was about 38.04% of total registered cases. Similar results have been demonstrated too in the study of Shehan Sharon and cols in 2011.[12]

Some protocols use 10 U of oxytocin and intravenous infusion to diminish surgical and postsurgical bleeding.[8,16] 5, 10, 15, 20 and 30 U of oxytocin in infusion have been used after umbilical cord ligation at 120 ml/h to diminish bleeding.[8] Some authors report that cardiovascular effects after oxytocin administration are only presented with high doses in a short time, and that obstetric doses don't change significantly arterial blood pressure.[8]

The cardiovascular effects seem to be related to doses and infusion rate. Unfortunately, previous studies from 2002 to 2011 don't specify bolus speed administration, without a clear definition of "slowly administration" speed. There is a lack of research about administration speed.[15]

Weaknesses of this study include that chest pain or discomfort are subjective data, symptoms that depends on patient perception. Another one is the electrocardiographic changes interpretation after oxytocin administration because it depends on the anesthesiologist experience in real time electrocardiography interpretation. This is a difficult work because it represent dynamical changes and could not be detected with enough detail in the display.

For this reason, in future studies we suggest the complementary analysis of cardiac enzymes and printed electrocardiograph in cases of chest pain reported by patients, with subsequent cardiology specialist interpretation to assess correct diagnosis and discard another chest pain diagnosis.

Oxytocin dose in bolus could be reduced significative in healthy women during elective caesarean operation, while effective uterine contraction stays. This modification in clinical practice would reduce adverse cardiovascular effects of this drug when is administered in high doses in bolus but may need some modification in placenta extraction technique.[4,5,15]

Oxytocin administration is not harmless as have been demonstrated in previous international studies. Incidence of chest pain, tachycardia and hypotension is directly related with oxytocin administration and the speed of this. Other adverse effects related with oxytocin administration are ST segment depression, flushing and discomfort. The habitual dose of 5U of oxytocin must be reduced and administered slower than actually by the hemodynamic changes produced. Adverse effects of any drug, in this case oxytocin, could be related with phenotypic characteristics of patients in study.

In future research it would be great to assess the minimal effective dose of oxytocin that could achieve the uterine contraction effectively and diminish bleeding during immediate postpartum period, and keep record of the infusion rate that could diminish the incidence of adverse cardiovascular effects.

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