

THE EFFECT OF INTRAVENOUS NITROGLYCERINE ON UTERINE RELAXATION IN EMERGENCY CESAREAN SECTION

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Abstract- Nitroglycerin has a relaxing effect on the smooth muscles of organs including uterus. This study investigates the effect of intravenous nitroglycerin in emergency cesarean sections in which rapid and transient uterine relaxation for rapid and nontraumatic extraction of the fetus is necessary. Sixty pregnant women who were been candidates for emergency cesarean and needed rapid uterine relaxation for different reasons were selected. These subjects underwent spinal anesthesia and at the time of uterine incision, 100 micrograms of nitroglycerin was injected to them intravenously. The time lapse between nitroglycerin administration and fetal extraction, the degree of uterine relaxation, the amount of intraoperative hemorrhage, uterine tone after fetal delivery and APGAR scores of the infants were all controlled and recorded. The results showed that in 53 (88.3%) of patients the uterus was acceptably relaxed and the fetus was delivered very easily. Only in 7 patients (11.7%) uterine relaxation was not acceptable. The mean decrease in systolic and diastolic blood pressures after nitroglycerin administration compared with before injection BP was 12.96 mmHg and 7.86 mmHg, respectively. There was not any prolonged effect of the drug such as uterus relaxation tone or abnormal bleeding. Also none of the delivered infants had low APGAR scores. Besides, in patients with acceptable uterine relaxation the first and fifth minute APGAR score of infants were higher ($P = 0.008$ and $P = 0.000$), respectively. This study shows that nitroglycerin can relax uterine smooth muscles very rapidly and transiently and in emergencies it can be an appropriate alternative to other tocolytic agents with prolonged effect or onset time.

Acta Medica Iranica, 44(6): 377-382; 2006

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Key words: Nitroglycerin, uterine relaxation, emergency cesarean

INTRODUCTION

Emergency cesarean section is often performed in situations such as unprogressive labor or arrest of descending part of the fetus, malpresentations including breech, transverse, and preterm labor, specially in association with fetal bradycardia. In these conditions, it is necessary to relax the uterine,

pharmacologically, in order to perform rapid and comfort fetal extraction and minimizing of trauma to the mother and her fetus (1, 2). Inhalational anesthetic agents have been used for uterine relaxation for several years (2); however, obstetric patients were considered as full stomach, because of physiologic changes of pregnancy and were exposed to hazardous complications of general anesthesia, such as pulmonary aspiration which is very dangerous and associated with high mortality rate. Halothane is an inhalational anesthetic with a good uterine relaxant effect, but it can cause unconsciousness and inhibit protective pharyngeal and laryngeal reflexes in a parturient who is under spinal

Received: 4 Jul. 2005, Revised: 14 Nov. 2005, Accepted: 19 Nov. 2005

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anesthesia and has not any protection such as tracheal intubation against aspiration (3, 4). It is noted that the choice anesthetic technique used for cesarean section is regional anesthesia, since general anesthesia has the risks of difficult or failed tracheal intubation or pulmonary aspiration (3). In this regard, using a drug, with rapid onset and short duration of action, without any effect on patient's consciousness was already considered. Nitroglycerin an effective and short-acting smooth muscles relaxant has been proposed for this purpose. It is an organic nitrate that was first used for angina pectoris in 19th century and today is generally used in cardiovascular settings (4). Nitroglycerin can relax vascular, bronchial, biliary tract, uterine and cervix smooth muscles actively. Recently using nitroglycerin in obstetric procedures, including uterine and cervical relaxation in cesarean, prevention of preterm labor, treatment of uterine inversion, cervical spasm and retained placenta has been reported (4-6). Vinatier *et al.* utilized intravenous nitroglycerin for internal podalic version of the second non-vertex twin in twin pregnancies (4) and Graigs conducted a trial of intravenous nitroglycerin in emergency cesarean for breech presentations (7). In none of these studies, any side effect of nitroglycerin was seen, such that intraoperative blood loss was in normal range and uterine tone returned to normal following administration of standard dose of oxytocin (4, 7). APGAR scores of neonates in the study of Vinatier *et al.* showed that there was not any problem in the neonatal APGAR scores (4). The aim of this study is utilization of intravenous nitroglycerin for rapid and transient relaxation for to nontraumatic fetal delivery, and on the other hand, not to expose the mother to the probable risks of inhalational drugs such as pulmonary aspiration or hemodynamic instability.

MATERIALS AND METHODS

In this uncontrolled clinical trial, 60 parturients were been candidate for emergency cesarean were selected using convenience sampling trial. All patients were in ASA class I and II without any limitation in age and parity. Emergency cesarean was done due to unprogressive labor, arrest of

descending or low station of the presenting part, malpresentations and twin or preterm pregnancies which needed to rapid and transient uterine relaxation to facilitate fetal delivery. Patients with preexisting cardiovascular or pulmonary disease, diabetics, mothers who required general anesthesia for different reasons and patients with the contraindications of regional anesthesia (patient refusal, shock and hypotension) were excluded from the study. After prehydration with 500-1000 ml of crystalloid, spinal anesthesia was performed using 25 gauge needle and 75-100 mg (1.5-2 ml) of 5% lidocaine from L3-L4 or L4-L5 interspaces. At the time of uterine incision, 100 µg nitroglycerin was injected intravenously. Vital signs including heart rate, arterial blood pressure and arterial O₂ saturation were controlled and recorded before and every minute after spinal anesthesia, before and after nitroglycerin administration and every 5 minute thereafter, using automated noninvasive devices. Any decrease in BP more than 20% from baseline was treated with 5-10 mg ephedrine IV, and repeated dosage as needed. All patients received an infusion of 10 unit oxytocin immediately after neonatal birth. After nitroglycerin injection, uterine relaxation which showed comfort of the obstetrician in fetal extraction was assessed using linear analog scale (LAS) (8) with manual percussion of the uterus by the obstetrician. This method was scored from zero to ten (0 = complete relaxation, 10 = complete tonicity). The intermediate scores were assessed by the obstetrician and recorded. Intraoperative blood loss was determined by measuring the aspirated blood from operative field in suction device (aspirator), and the amount of bloody sponges and laparotomy packs. Each complete bloody sponge was calculated to have about 10-15cc blood and each laparotomy pack about 100-120cc. The time lapse from uterine incision and fetal extraction, intraoperative hemorrhage and uterine tone (according to LAS) after fetal delivery and 1 and 5 minutes APGAR scores of the infants were controlled and recorded.

All data were entered into SPSS software for statistical analysis and were expressed as mean ± SD (standard deviation). Data of BP before and after nitroglycerin administration were compared using

paired *t* test. According to LAS, patients were allocated in group 1 as acceptable uterine relaxation (LAS 0-4) and group 2 as unacceptable uterine relaxation (LAS > 4) and all data including neonatal birth time, intraoperative blood loss, uterine tone and 1 and 5 minutes APGAR scores were compared in two groups using independent *t* test. Statistical significance was declared when $P < 0.05$.

RESULTS

38 patients (63.33%) were nulliparas, 14 patient were in second and 8 patient in third and fourth gravidity. Maximum gravidity was found to be four in this study. Indications for cesarean section were malpresentation in 37 parturients (61.7%) and unprogressive labor or low station in 23 (38.3%). Table 1 shows demographic data of 60 parturients. The effect of nitroglycerin on uterine relaxation was assessed with LAS and from 60 parturients, in 53 (88.3%) patients uterine relaxation was 0-4 which were assigned to acceptable relaxation (group 1) and only 7 (11.7%) patients had LAS > 4, assigned as unacceptable relaxation (group 2). Systolic and diastolic hypotension after nitroglycerin administration compared with before injection BP was statistically significant in all patients and these results showed the vasodilatory and hypotensive effects of nitroglycerin even in lower doses. However, mean decrease in systolic and diastolic arterial pressures were 12.97 mmHg (12.210%) and 7.86 mmHg (12.208%), respectively (Table 2) and only 9 patients (15%) received ephedrine 5-10 mg

Table 1. Demographic data of the studying patients

Variable	Min	Max	Mean	SD
Age (yr)	17	39	26.62	5.46
Weight (kg)	50	86	69.08	8.69
Gravidity	1	4	1.50	0.77

Abbreviation: SD, standard deviation.

as vasopressor for increasing blood pressure and preventing probable hemodynamic instability.

The difference in heart rate and arterial O₂ saturation before and after nitroglycerin injection were not significant as showed in table 2. nitroglycerin had not any significant effect on uterine tone after delivery, such that in 58 patients (96.66%) uterine tone LAS was >7 and in 2 patients (3.33%) was LAS was < 7 after neonatal birth. Uterine bleeding was acceptable for cesarean section in all patients and none of them had abnormal intraoperative hemorrhage (table 3). The time lapse from nitroglycerin administration and fetal delivery was less than 3 minute in 49 patients and in 11 patients was higher than 3 minute.

From 49 patients, 44 were in group 1 (acceptable relaxation) and 5 in group 2 (unacceptable relaxation). From 11 patients, 9 patients were in group 1 and two were in group 2. Comparing of the two groups (1 and 2), there was not any significant difference in uterine bleeding and tonicity after fetal delivery. Also evaluation of the neonatal APGAR scores as shown in table 1 and comparing the 1st and 5th minute APGAR scores of the infants in group 1 and 2 showed that all neonates had high APGAR score, besides neonates of group 1 had higher 1st and 5th minute APGAR score than group 2 (Table 4).

Table 2. Hemodynamic changes before and after nitroglycerin injection in studying patients

Variable	Min	Max	Mean	SD	<i>P</i> value* (2-tailed)
Sys BP before TNG	90	148	106.22	12.97	0.0009
Sys BP after TNG	50	90	64.38	9.06	
Dis BP before TNG	65	130	93.25	13.68	0.019
Dis BP after TNG	30	85	56.52	9.64	
Difference of Sys BP after and before TNG	0	35	12.97	8.16	0.0001
Difference of Dis BP after and before TNG	0	25	7.86	11.07	0.0001
HR before TNG	62	117	85.68	15.58	0.924
HR after TNG	60	116	82.82	14.24	
SaO ₂ before TNG	96	99	97.93	1.032	0.947
SaO ₂ after TNG	96	99	98.88	0.883	

Abbreviations: Sys, systolic blood pressure; Dis, diastolic blood pressure; HR, heart rate; TNG, nitroglycerin; SaO₂, arterial O₂ saturation.

* $P < 0.05$ is significant.

Table 3. Study data after nitroglycerin administration

Variable	Min	Max	Mean	SD
Uterine relaxation (LAS)*	0	9	2.48	2.05
Time from uterine incision to fetal birth (min)	1.5	4.5	2.500	0.823
Hemorrhage (cc)	1000	1800	1174.17	176.71
Uterine tone after fetal birth (LAS)	3	10	8.57	1.32
1 st min APGAR score	7	9	8.73	0.48
5 th min APGAR score	9	10	9.88	0.32

Abbreviation: LAS, linear analogue scale.

DISCUSSION

Since the first synthesis of nitroglycerin in 1846, many usages have been recorded. The vasodilatory properties of both nitroglycerin and amyl-nitrite have been used to relieve angina pectoris since the middle of the nineteenth century. The safety, predictability and ease of intravenous administration of this drug have been firmly documented. Smooth muscles of bronchial, biliary, gastrointestinal and urinary tracts are affected by this drug. It relaxes uterine smooth muscles actively and because smooth muscles constitute 10% - 15% of cervical tissues, cervix is also relaxes partially (2). Usually a rapid general anesthesia associated with inhalation of a halogenated agent provides both a good analgesia and uterine relaxation. However, this protocol is both hazardous and time consuming since it requires induction and tracheal intubation of a full-stomach

patient. The concentration of an inhalational drug necessary to relax the uterus may depress the cardiovascular system and at a time hemodynamic may be unstable (3, 4). While uterine relaxation occurs within 30-90 second after intravenous administration of nitroglycerin and lasts about 1 minute, the half life of nitroglycerin in adults is 1-3 minute (4). In this study, in 53 patients (88.3%) according to LAS, uterine relaxation was 0-4, means that it was complete to acceptable and the fetus delivered comfortably, without any problem. Only in 7 patients (11.7%) the uterine tone was between 5-10 and from them, 4 cases had LAS 5-7 and 3 cases had LAS 8-10. In these 3 patients, supplementary inhalational halothane was used to further facilitate fetal extraction but for 4 cases with LAS 5-7 the fetus delivered with a minimally more efforts and there was not need for supplementary halothane. In this base, the patients enrolled in one of the two groups, of acceptable relaxation (LAS, 0-4) and unacceptable relaxation (LAS > 4). Assessment of hemodynamic changes (BP, HR) and the amount of arterial O₂ saturation showed that systolic and diastolic hypotension after nitroglycerin injection compared with before injection BP were 12.12% and 12.2%, respectively.

Since blood pressure changes in the range of 20% from baseline are acceptable (3), thus these changes were not associated with any problem. In 52 patients (86.2%) blood pressure normalized spontaneously with continuing crystalloid infusion and in 9 patients ephedrine 5-10 mg was effectively used as vasopressor. Heart rates and arterial O₂ saturation were in normal range before and after nitroglycerin administration and throughout surgery. Graigs *et al.*

Table 4. Comparing of mean and standard deviation of clinical parameters after nitroglycerin administration in patients with acceptable and unacceptable uterine relaxation*

Study group	Time from TNG injection	Uterine bleeding	Uterine tone (LAS)	1 st min APGAR score	5 th min APGAR score
	to fetal birth (min)				
Group 1 (n = 53) (acceptable)	2.34 ± 0.8	1172.6 ± 161.3	8.5 ± 1.4	8.8 ± 0.4	9.9 ± 0.2
Group 2 (n = 7) (unacceptable)	3 ± 0.8	1185.7 ± 285.4	8.7 ± 0.9	8.29 ± 0.8	9.4 ± 0.5
P value (t test)†	0.87	0.85	0.75	0.008	0.000

Abbreviations: TNG, nitroglycerin; LAS, linear analogue scale.

* Data are given as mean ± standard deviation.

† P < 0.005 is significant.

report a prospective study of using 400-800 µg nitroglycerin sublingually to induce uterine relaxation. The mean maximal systolic blood pressures drop was 18% of systolic pressures prior to drug administration, without any problem to the mother (7). In the study of Vinatier *et al.* who used intravenous nitroglycerin for internal podalic version of the second non-vertex twin in 10 parturients, there was not any hemodynamic instability (4).

In our study, the time lasts from nitroglycerin injection (uterine incision) to complete fetal delivery was 3 minute or lower in 49 patients and higher than 3 minute (maximum 4.5 minute) in 11 patients. In the later 11 patients, 9 patients were in group 1 and 2 in group 2. The reason for delayed extraction was breech presentation in 10 patients, whereas trapping of the fetal head behind the partially dilated cervix and in one case arrest of the descending part of the fetus with the low station of it delayed fetal delivery. There was no significant difference in birth time between two groups. In the study of David *et al.* on 55 case of cesarean section, 200 µg nitroglycerin was applied prophylactically for delivery of preterm infants weighting 500 to 1500 g. In 42 patients the time interval between drug injection and cutting of umbilical cord was 3 minutes or lower and in 13 cases was higher than 3 minute (9).

In this study, intraoperative hemorrhage was in the normal range of 1000-1800 ml for cesarean section and there was not any delayed relaxant effect of nitroglycerin on the uterine tone and increased blood loss. Also uterine tonicity, after fetal delivery and routine infusion of 10 units oxytocin was 7-10 in 58 patients (96.6%) and 3-5 in two (3.33%) patients. In these two patients uterine tone returned to normal following receiving an additional 10 units of oxytocin. The other studies have also shown similar results of intraoperative bleeding and uterine tone following administration of the standard dosage of oxytocin (4, 7).

In spite of emergency surgery and the risk of fetal hypoxemia, the 1st minute APGAR scores were between 7-10 for all neonates. Scores of 7-8 improved to 9-10 with simple and initial resuscitation trial. These 7-8 APGAR scores were related to prematurity and twin pregnancy. In addition, comparing the APGAR scores of infants of the two groups, showed that mean APGAR scores of the neonates of group 1 were higher than group 2.

Theoretically, the low molecular weight and uncharged state of nitroglycerin should facilitate transplacental passage of the drug. Wheeler showed that in sheep, an infusion of nitroglycerin produced a decrease in maternal blood pressure, but no changes in uterine blood flow or in uterine vascular conductance was observed (10). In the study of Vinatier *et al.*, there was not any adverse effect of nitroglycerin or on uteroplacental circulation, APGAR score of neonates or umbilical artery blood gases (4).

These low fetal nitroglycerin concentrations could be due to rapid fetal drug metabolism (4). Matthias *et al.* used 0.25-0.5 mg intravenous nitroglycerin for cesarean section and reported that nitroglycerin and its metabolites' levels in the umbilical plasma was 2-3 times lower than the mothers' plasma. Also, arterial blood pressure, pulse rate and 1st, 5th and 10th minute APGAR score of neonates were in the normal range (11). David *et al.* found that administration of nitroglycerin to facilitate the extraction of the preterm infants lower than 32 weeks of gestation, had no adverse effect on neonatal APGAR scores and umbilical artery pH values (7.10 or lower) compared with the neonates delivered from mothers who have not received nitroglycerin (9). In another study, nitroglycerin patches was applied transdermally for 50 parturient in 16 to 32 weeks of gestation for preventing premature uterine contraction and premature delivery. There was not any adverse effect on neonates delivered later (12).

With regard to this study, it appears that nitroglycerin can be used in obstetrician field due to its rapid onset and short duration of action but we suggest that it is necessary to study more about it, especially in the face of clinical controlled trial and comparing this drug with other tocolytics, to achieve more and better results in order to was it more safely in clinical trials.

Acknowledgements

With special thanks to anesthesia personnel of Alzahra hospital for their contribution to this study.

Conflict of interests

The authors declare that they have no competing interests.

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