

## A randomized clinical trial to compare the effectiveness of two different doses of intravenous Nitroglycerine for manual removal of placenta

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### Abstract

**Introduction:** After the birth of the baby if the placenta is not expelled within 30 minutes of the delivery, it is termed as retained placenta. The incidence of retained placenta is 2% of deliveries world-wide and is an important cause for maternal mortality and morbidity. Nitroglycerine (NTG) is an organic nitrate that relaxes smooth muscles and produces a generalized vasodilatation. As it relaxes the smooth muscle, it is also used as a uterine relaxant for manual placental removal.

**Aims and Objectives:** To know the efficacy and safety of intravenous NTG in manual removal of placenta and to know the hemodynamic effects during the procedure.

**Materials and Methods:** Total number of patients included in this study were 40. Patients were divided in two groups, each group having 20 patients each. Group 1 patients were administered with 100 microgm of NTG and group 2 patients with 150 microgm of NTG. Clinical parameters and complications were studied and compared between the two groups. Placenta was observed for separation and graded as easily separated, separated with assistance, difficult to separate, failed to separate. The clinical parameters like hypotension, tachycardia, headache after awakening, palpitation after awakening were compared between the two groups.

**Results:** In group 1, we observed that placenta was easily separated in 12 patients (60%), separated with assistance in 3 patients (15%), difficult to separate in 3 patients (15%) and in 2 patients (10%) placenta was not separated. In group 2, we observed that, placenta was easily separated in 14 patients (70%), separated with assistance in 2 patients (10%), difficult to separate in 2 patients (10%) and in 2 patients (10%) placenta was not separated.

**Conclusion:** Intravenous NTG is an effective and safe method for manual removal of placenta with a dose of 100 microgram.

**Keywords:** Intravenous, Nitroglycerin, Retained placenta.

### Introduction

Delivery of the placenta is called as third stage of labour. After the birth of the baby if the placenta is not expelled within 30 minutes of the delivery, it is termed as retained placenta.<sup>1</sup>The expulsion of the placenta occurs due to contraction of the retroplacental myometrium and placenta should shear away from its bed and expelled.<sup>1,2</sup>The incidence of retained placenta is 2% of deliveries world-wide and is an important cause for maternal mortality and morbidity.<sup>3</sup> The mortality due to retained placenta constitutes to 10% in the developing world. Timely management with appropriate treatment is very important to save the life.<sup>4</sup>

Nitroglycerine (NTG) is an organic nitrate that relaxes smooth muscles and produces a generalized vasodilatation.<sup>1</sup> Intravenous infusion of nitroglycerine (5-15 mcg/min) is widely used in anesthetic practice for managing patients with acute decompensated heart failure, perioperative myocardial ischemia and for achieving hypotensive anesthesia.<sup>2,3,5</sup> As it relaxes the smooth muscle, it is also used as a uterine relaxant for manual placental removal, when the other measures fail to achieve the same.

Sequential administration of oxytocin and nitroglycerine is used to achieve the desired effect when the conventional dose of oxytocin fails to achieve the

same. NTG can be administered through sublingual route (1 mg) or intravenous boluses (50-100 mcg) to achieve the desired effect. The complications after the administration of NTG are hypotension, tachycardia and headache are known from decades. Hypoxia is also a known potential complication, which is due to the nitroglycerine induced vasodilatation leading to alteration in the protective hypoxic pulmonary ventilation. Hypoxia as a complication is known to occur with continuous infusion of nitroglycerine compared to IV bolus dosages which is frequently required in obstetrics.<sup>4,6</sup> Many studies are available suggesting the effective use of sublingual NTG in manual removal of placenta. In our study we have compared the effects and complications of IV NTG in two different doses that is 100 and 150 micrograms in achieving the desired effect for manual removal of placenta.

### Aims and Objectives

To know the efficacy and safety of intravenous NTG in manual removal of placenta and to know the hemodynamic effects during the procedure.

## Materials and Methods

This study was a prospective, randomised (by simple random method using lottery method) conducted in Shri B M Patil Medical College and Research Centre, Vijayapura. As the incidence of manual removal of placenta is very rare, we have included 40 patients in our study based on last year statistics in our hospital. These patients were divided in two groups having 20 patients each. Group 1 were administered 100 microgram of NTG and group 2 with 150 microgram of NTG. Clinical parameters and complications were studied and compared between the two groups.

**Inclusion Criteria:** Healthy pregnant ASA I and II patients, with at least 36-40 weeks of gestation

**Exclusion Criteria:** Pregnancy induced hypertension, postpartum hemorrhage requiring immediate intervention, uterine malformation, intolerance to nitroglycerine, maternal age less than 18 years, serious maternal disease.

After doing pre-anesthetic evaluation, patients were shifted inside the operation theatre with large bore IV line without preloading, Standard monitor was applied and baseline vitals were noted. Premedication was given with inj glycopyrolate, inj midazolam 1 mg and fentanyl 100 microgram. Patients were induced with inj Ketofol (ketamine 1mg/kg plus propofol 1 mg/kg). Adequate size of pro-seal LMA was inserted and checked for proper position and air entry.

**In Group 1:** After giving 100 microgram of IV NTG, procedure was allowed to start after two minutes. Observed for the separation of placenta and response

from the surgeon. If placenta was not separated easily, repeat dose of NTG 50 microgram IV was given.

**In Group 2:** we had given 150 microgram NTG intravenously and rest all steps were same as mentioned above. If manual removal of placenta was unsuccessful in both the groups, we have adopted alternate method for manual removal by giving volatile anesthetic Isoflurane 1%.

Intraoperatively all patients were monitored for ECG, HR, NIBP, SpO<sub>2</sub> and EtCO<sub>2</sub> every five minutes. We have observed for side effects like hypotension (BP less than 90/60 mm of Hg), tachycardia (more than 90 per min), headache and palpitation after awakening. When hypotension occurred, it was treated by inj ephedrine and bolus infusion of IV fluids.

If arrhythmias occur we have to treat antiarrhythmic drugs.

Removal of placenta was grouped into four categories, 1) Easily separated 2) Separated with assistance manually 3) Difficult to separate 4) Not able to separate. Immediately after removal, 10 units of oxytocin was added to IV fluid. If uterus was not contracting, then after consultation with operating surgeon inj methargine was given for adequate contraction. Postoperative monitoring of HR, SpO<sub>2</sub> and, NIBP was done. We have compared the side effects of the drug like heart rate, blood pressure, saturation, palpitation and headache after awakening between the two groups

## Results

**Table 1: Clinical parameters of the patients who participated in the study**

Parameters	NTG 100 µgm (Group 1) (N 20)	Percentage (%)	NTG 150µgm (Group 2) (N 20)	Percentage (%)
Age of mothers	25 to 35years	100	25 to 35years	100
Gestational age in weeks	36 to 40	100	36 to 40 wks	100
Type of anaesthesia	General anaesthesia with pro-seal LMA	NA	General anaesthesia with pro-seal LMA	NA
Successful delivery of placenta	15	75	18	90
Second dose required for removal	5	25	NA	NA
Alternate method used	2	10	2	10

**Table 2: Distribution of patients according to grading of separation of placenta.**

	Group 1	Percentage%	Group 2	Percentage%
Easily separated	12	60	14	70
Separated with assistance	3	15	2	10
Difficult to separate	3	15	2	10
Failed to separate	2	10	2	10

In group 1 we observed that placenta was easily separated in 12 patients (60%), separated with assistance in 3 patients (15%), difficult to separate in 3 patients

(15%) and in 2 patients (10%) placenta was not separated.

In group 2, placenta was easily separated in 14 patients (70%), separated with assistance in 2 patients

(10%), difficult to separate in 2 patients (10%) and in 2 patients (10%) placenta was not separated.

**Table 3: Complications with the use of NTG in both the groups**

Complications	NTG (group1)100µgm (N 20)	Percentage (%)	NTG(group2) 150µgm (N 20)	Percentage (%)
Tachycardia	05	25	10	50
Hypotension	12	60	16	80
Desaturation	Nil		Nil	
Arrhythmias	Nil		Nil	
Palpitation after awakening	01	05	02	10
Headache after awakening	01	05	04	20

### Discussion

The incidence of retained placenta is 2-3.3%, which occurs as a complication in vaginal deliveries.<sup>7</sup> Failure of retro placental myometrial contractions is the most common cause for retained placenta. Hemorrhage can be life threatening if not managed immediately. Oxytocin is administered conventionally, if it fails then administration of oxytocin and nitroglycerine is preferred sequentially for the management.<sup>8</sup> The advantage of the use of nitroglycerine is that it has rapid onset of action (75-95 seconds) with effective uterine relaxation and compared to the presently available tocolytics. NTG can be administered through sublingual route (1 mg) or intravenous boluses (50-100 mcg) to obtain the optimum desired action. But few side effects have been reported with the use of intravenous nitroglycerine. Hypotension, tachycardia and headache are usual side effects. Hypoxia is a potential complication reported with the intravenous use of nitroglycerine. Attenuation of protective hypoxic pulmonary ventilation drive due to the vasodilatation caused by NTG is the main mechanism for hypoxia.<sup>9</sup> Hypoxia is reported as a side effect with continuous infusions (5-15 mcg) but bolus dosages frequently administered in obstetrics has no such side effect.

In our study, totally 40 patients were administered with NTG intravenously, 20 in each group. The patients age ranged from 25 to 35 years in both the groups. The gestational age of the patients in both the groups were between 36 to 40 weeks. General anesthesia with Proseal LMA was used for each case. In group 1 with the administration of 100 microgram of NTG, successful delivery of the placenta was observed in 75% of the patients whereas in Group 2, it was observed in 90% of the patients. In a study titled "Nitroglycerine for Rapid tocolysis -development of a Protocol and a Literature Review" by Grady JP et al,<sup>10</sup> 100% successful delivery of the placenta was observed with 150 microgram NTG. These results were comparable with our study.

In Group 1, 5 patients received second dose of NTG with 50 microgm for successful removal of placenta constituting to 25%. Whereas in Group 2 we have not given second dose. For both groups, second

alternative method was used when above method failed. Campbell et al<sup>11</sup> in 1999 in their study titled "Emergent uterine relaxation with intravenous nitroglycerine for a vaginal breech delivery: clinical report and review" have used volatile anesthetics administered via an endotracheal tube following a rapid sequence induction of general anesthesia and intubation. In our study, after giving 150 microgram NTG if manual removal of placenta was unsuccessful, then we used volatile anesthetic for removal.

In both groups, 10% of patients received alternative method for manual removal of placenta without any complications. Generalized vasodilatation may cause profound hypotension and reflex tachycardia. Hypotension is particularly likely in patients with compromised preload. Patients who sustain hypotension after being administered nitroglycerine should have all sources of nitroglycerine removed, and should receive a normal saline fluid challenge [250cc]. In group 1, five patients developed tachycardia constituting to 25% whereas in group 2, it was observed in ten patients (50%).

12 patients (60%) developed hypotension in group 1, whereas 16 (80%) patients in group 2. During hypotension, patients were treated with fluids and ephedrine 3 mg intravenously.

None of the patients had arrhythmias with the use of NTG in both the groups.

When the patients were awake after the procedure, one patient (5%) from group 1 complained of headache but four patients (20%) had headache in group 2.

Palpitation developed in one patient (5%) in group 1, whereas in group 2 it was seen in four patients (20%).

Axemoetal<sup>12</sup> in their study with the use of 100-200 microgm of intravenous NTG in 22 patients for manual removal of placenta, reported that hemodynamic side effects due to NTG were clinically insignificant.<sup>12</sup>

In a study conducted by Lowenwirtetal,<sup>13</sup> they used IV NTG in a dose of 50-100 microgms for manual removal of placenta in 33 patients. They observed a minimal change in hemodynamic system.<sup>13</sup>

Peng et al<sup>14</sup> in their study with the use of 500 microgm intravenous NTG, for manual removal of

placenta in 15 patients, they observed insignificant decline in systolic and diastolic pressures.<sup>14</sup>

### Conclusion

Intravenous route of NTG is an alternative method for manual removal of placenta due to its short half-life and rapid onset of action. Successful removal of placenta was achieved with both the dosages of IV NTG (100 and 150 microgm) with minimal side effects. Thus, dose of 100 microgm can also be a safe and effective alternative method for manual removal of placenta with minimal haemodynamic changes.

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