Use of Sublingual Nitroglycerin in Management of Retained Placenta after Second Trimesteric Abortion

Hosam M. Hemeda, Magdy M. Kamal and Hanan M. Eldeeb

Department of Obstetrics and Gynecology, Faculty of Medicine, Ain Shams University Cairo, Egypt
Hosam1973md@gmail.com

Abstract: Background: retained placenta is defined as lack of expulsion of the placenta 30 minutes after delivery of the fetus. It occurs in about 2.0-3.3% of all mid trimesteric abortions. For management of retained placenta, oxytocin administration combined with controlled umbilical cord traction is usually done. Oxytocin is either administered intravenously or into umbilical vein. After failure of the above procedures, operative manual removal under anesthesia is necessary. General anesthesia is preferred as it provides both good analgesia as well as adequate cervico-uterine relaxation. However general anesthesia may have some hazards. Several reports have indicated that intravenously administered nitroglycerin is effective for successful delivery of retained placenta. Nitroglycerin is a well known nitric oxide donor. Nitric oxide donors including nitroglycerin induce rapid relaxation of the pregnant myometrium as well as the uterine cervix. Aim of the work: to investigate the efficacy and safety of sublingual nitroglycerin in the management of midtrimesteric abortion retained placenta. Patients and methods: prospective double-blind randomized controlled clinical trial. 40 women with retained placentae after mid-trimesteric abortion were recruited for the study randomized into 2 groups: First group received nitroglycerine1 mg sublingual and the second group received placebo. Results: 19 women (95%) in the group of patients received nitroglycerin had successful delivery of placenta within 10 min of gentle controlled cord traction and only one woman (5%) required operative manual removal of placenta under general anesthesia. In the group of patients received placebo, out of 20 women, only 4 women (20%) had successful delivery of placenta. For the other 16 women (80%) in this group operative manual removal of placenta under general anesthesia was necessary. time elapse till placental delivery was longer in the control group. Neither the patients received nitroglycerin nor the patients received placebo develop post abortive bleeding affecting the general condition.
Conclusion: Sublingual nitroglycerin in association with oxytocin is a safe and effective drug in management of mid-trimesteric abortion retained placenta.
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Key words: Nitroglycerin, Mid-trimesteric Abortion, Post abortive bleeding.

1.Introduction

Retained placenta is defined as failure of expulsion of the placenta 30 minutes after delivery of the fetus [(1)] .The incidence of retained placenta is approximately 2.0-3.3% of all mid trimesteric abortion Worldwide.[(2)]

The management of retained placenta starts with oxytocin administration either intravenously or into umbilical vein combined with controlled umbilical cord traction. [(3)]

According to a recent Cochrane review, umbilical vein injection of diluted oxytocin via nasogastric tube appears to be effective for management of the retained placenta [(4)] .

After failure of the above procedures, operative manual removal under anesthesia is necessary. General anesthesia is preferred as it provides both good analgesia as well as adequate cervico-uterine relaxation. However gereral anesthesia may have some hazards [(5)] .

Traditionally, retained placenta after second-trimester abortions has been managed by instrumental removal and curettage with general anesthesia, which may be associated with hemorrhage, infection, and uterine perforation. Medical management to facilitate the delivery of the retained placenta is a safe alternative that avoids surgical intervention [(6)].

The ***Royal College of Obstetricians and Gynecologists*** (RCOG) guidelines, (2004) stated that surgical evacuation of the uterus after second trimester abortions is not routinely required, and should only be performed in case of a retained placenta, severe blood loss, or when a placental remnant is suspected based on combination of clinical symptoms and ultrasonographic assessment of the uterine cavity. Likewise, the Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) guidelines, (2005) recommend surgical evacuation only in case of acute clinical symptoms, such as persistent heavy bleeding, and surgical evacuation based on ultrasonographic assessment of the uterine cavity[(7)] .

O'Brien et al. reported that sustained uterine contractions were produced within 3 minutes after rectal administration of 8oo µg of misoprostol, a

synthetic prostaglandin E1 was important for expulsion of the placenta after second trimester abortions, well tolerated with less side effects and no complications. And concluded that this method should be tried before surgical intervention[8] .

Several reports have indicated that intravenously administered nitroglycerin is effective for successful delivery of retained placenta [9] .

Nitroglycerin is a well known nitric oxide donor. In vitro, nitric oxide donors including nitroglycerin induce immediate relaxation of the pregnant myometrium as well as the uterine cervix [10] . *In vivo*, rapid uterine relaxation of short duration is obtained following intravenous injection of 100-200µg nitroglycerin [11] .This rapid relaxation may be beneficial in the delivery of retained but separated placenta.

The use of sublingual nitroglycerin as an alternative to intravenous route was tried in previous studies and appears to be of similar efficacy, with higher safety profile and with more patient compliance.

2.Patients and methods

This study is a prospective double-blind randomized controlled clinical trial. A total number of 40 women were recruited for the study . The study was carried out at Ain Shams University Maternity Hospital (between May 2009 and May 2011).

All patients included in the study were with unscarred uterus having spontaneous midtrimester abortion (13-26 weeks) and with no known history of congenital uterine malformations

Retained placenta is defined as failure to deliver the placenta after 30 minutes of abortion of fetus. [12] . Patients excluded from the study were those who had postabortive hemorrhage requiring immediate intervention and those with known congenital uterine malformations.

Immediately, after spontaneous abortion of the fetus, oxytocin (Syntocinon®) 5 units IM given and if the placenta was separated and felt by P/V in the vagina, gentle controlled cord traction was carried out. If the placenta remains undelivered 30 minutes after expulsion of the fetus, an additional dose of 10 IU oxytocin was given intravenously to induce more efficient uterine contractions and thus promote placental separation. Five minutes after administration of the 2nd dose of oxytocin, placental delivery will be expected. Women were considered eligible for recruitment to the study if the placenta remained undelivered 40 minutes after abortion of fetus despite additional administration of 10 IU oxytocin followed by gentle controlled cord traction.

Once the diagnosis of retained placenta is established, a rapidly running intravenous infusion of Ringer's lactate solution was initiated and all women were hemodynamically monitored and antibiotics were given.

The study group was randomized to either of the two groups:

Group One: Twenty women with retained placenta were given 1mg of nitroglycerin tablets sublingually.

Group Two: Twenty women with retained placenta were given two placebo tablets of similar design as the nitroglycerin tablets.

The drug used in this study was synthesized in Pharco pharmaceutical company and composed of 0.5mg nitroglycerin per tablet.

The placebo used in this study was synthesized also in Pharco company and composed of inert material (starch) and has the same shape and physical characters as nitroglycerin tablets.

The tablets were administered sublingually and after five minutes of their administration of nitroglycerin or placebo tablets, gentle controlled cord traction was performed for a maximum duration of 5 min. No anesthesia was given during this procedure. Additional intravenous oxytocin 5 IU was given once the placenta is delivered. The tablet was removed after delivery of the placenta if remnants of the tablet are still present in the patients' mouth.

The time elapsed between the administration of the drugs and delivery of the placenta was recorded (maximum time 10min).

If the placenta remained undelivered, operative manual removal was conducted under either regional (spinal) or general anesthesia (according to the protocol of the setting).

Maternal blood pressure and pulse rate measured immediately prior to the sublingual administration of the tablets and every 5minutes later for assessment of possible homodynamic effects caused by nitroglycerin tablets.

Possible side effects of nitroglycerin were recorded e.g. headaches, hypotension, facial flushing , tachycardia and post abortive hemorrhage.

If post abortive hemorrhage developed further ecbolics was administrated e.g. methyl ergonovin (methergin) 0.2mg I.M or misoprostol 400-600 microgram rectally.

3. Results

There was no significant difference between both groups as regards the age, gestational age and parity. ***Table (1).***

Among the group of patients randomly received nitroglycerin (n=20) 19 women successfully expelled the placentae (95%) and only one woman required instrumental removal of the placenta while in the placebo group (n=20) only 4 women could deliver the placenta (20%) and the rest (80%) needed

instrumental placental delivery. This difference was highly statistically significant (p<0.001).

Table (1)	***Cases N=20 Mean SD***	***Control N=20 Mean SD***	***P***
Maternal Age (years)	27.7 4.4	28.5 5.2	0.6
Gestational age (weeks)	16.8 4.1	17.6 3.9	0.5
	Cases N=20 Median IQR	***Control N=20 Median IQR***	***p***
Parity	3 2	3 2	0.758

Comparing the time interval between administration of the drug and placental expulsion in both groups shows also a high statistical significance (p<0.001) the mean time interval in the nitroglycerin group was 3.2 ± 1 minutes while in the placebo group it was 9.3 ±0.4 minutes.

Headache developed in 9 patients of the nitroglycerin group (45%) and in 12 patients of the placebo group (60%) (p=0.3).

Palpitation developed in 5 patients of the nitroglycerin group (25%) and in 4 patients of the placebo group (20%) (p=0.7).

Blood pressure changes before and after drug administration shows non significant difference regarding the drop in the systolic blood pressure in both groups with a mean drop of 14.7 ± 4.9 mmHg in the nitroglycerine group and 15.7 ± 5.9 mmHg in the placebo group.(p=0.5).Regarding diastolic blood pressure drop in both groups there was found a significant statistical difference. The mean drop in the diastolic blood pressure in the nitroglycerine group was 12.5 ± 5 mmHg while in the placebo group was 1.5±1 mmHg (p=0.001).

pulse changes before and after the tablet administration showed significant change between both groups the mean rise in pulse in the nitroglycerine group was 2 ± 3.5 beats/min while there was a drop in the pulse in the placebo group with a mean pulse drop 1.7 ± 3.6 beats/min.(p=0.02)

All these hemodynamic changes were mild not affecting the general condition of the patients in both groups.

Neither the patients received nitroglycerin nor the patients received placebo develop post abortive bleeding affecting the general condition or requiring blood transfusion.

4.Discussion

Previous reports have indicated that intravenously administered nitroglycerin is effective for successful delivery of retained placenta [(9)]

When nitroglycerin is injected intravenously, uterine relaxation usually occurs within 45-60s and the relaxation normally lasts no longer than 2min [(11)].

In contrast, sublingual nitroglycerin reaches its maximum plasma concentration within 5 min with a half-life of approximately 3min [(13)].

This observation is in agreement with the fact that vasorelaxation induced by sublingual nitro-glycerin for treatment of angina pectoris normally occurs within 2-3min following sublingual administration. Furthermore, a dose of 1 mg nitroglycerin, as used in the present study is a standard dose for treatment of angina pectoris. [(13)]

This study was performed, to test the effect of sublingual nitroglycerin tablets and placebo tablets in management of mid-trimesteric abortion retained placenta (trapped placenta).

The present study showed that: 19 women in the group of patients received nitroglycerin(n=20) (95%) had successful delivery of placenta within 10 min of gentle controlled cord traction (with the mean time 3.2 min). Only one woman (5%) in this group, required operative removal of placenta.

This result is in agreement with ***Ekerhovd and Bullarbo*** [(10)] who examined the success rate and safety of sequential administration of intravenous oxytocin in combination with sublingual nitroglycerin for the delivery of retained placenta. And found that twenty-one out of twenty four women delivered the placenta successfully following sublingual administration of nitroglycerin. The procedure failed in 3 women and operative manual removal under regional or general anesthesia was undertaken. No complications due to nitroglycerin were registered and conclude that: Sequential administration of oxytocin and nitroglycerin seems to be an effective and safe procedure in the management of retained placenta.

While, out of 20 women given placebo tablets, 4 women (20%) had successful placental delivery by means of gentle Controlled cord traction but time was more (mean time till placental delivery 9.3 min) For the other 16 women (80%) in this group operative removal of placenta under general anaesthesia was necessary.

Regarding the side effects of nitroglycerin, the most frequent one was headache, experienced by 9 women (45%). While, in the group of patients received placebo, 12 women (60%) reported headache within 10 min following administration of placebo tablets Furthermore, in all women, the headache disappeared spontaneously within 2 hrs.

This headache is subjective and may be attributed to insomnia of the patient, anemia, hypotension [(14)], chronic sinusitis [(15)], Headaches

emanating from sources in the cervical spine. ([16]

Nitric oxide (NO) may participate in the mechanisms underlying vascular headaches, such as migraine and cluster headache (CH), by triggering neurogenic inflammation and activation of fibres conveying nociceptive inputs to the trigeminal ganglion [(17)].

Five women (25%) in the group of patients received nitroglycerin and four women (20%) in the group of patients received placebo reported palpitation.(p=0.7).This palpitation can be attributed to anemia, dehydration, blood loss [(18)], gestational Palpitation [(19)] and cardiac disease [(20)] .

blood pressure changes before and after drug administration shows non significant difference regarding the drop in the systolic blood pressure in both groups with a mean drop of 14.7 ± 4.9 mmHg in the nitroglycerine group and 15.7 ± 5.9 mmHg in the placebo group.(p=0.5).Regarding diastolic blood pressure drop in both groups there was found a significant statistical difference. The mean drop in the diastolic blood pressure in the nitroglycerine group was 12.5 ± 5 mmHg while in the placebo group was 1.5±1 mmHg (p=0.001).

Pulse changes before and after the tablet administration showed significant change between both groups the mean rise in pulse in the nitroglycerine group was 2 ± 3.5 beats/min while there was a drop in the pulse in the placebo group with a mean pulse drop 1.7 ± 3.6 beats/min.(p=0.02)

All these hemodynamic changes were mild not affecting the general condition of the patients in both groups.

These results are in disagreement with ***Chedraui and Insausti (2003)*** [(9)] who examined the use of intravenous nitroglycerin in the management of retained placenta and found that, a significant decrease in systolic and diastolic blood pressures measured 15 min after administration of the drug as compared to immediately before administration of nitroglycerin. In the placebo group a significant decrease in systolic blood pressure was registered. While a slight increase in pulse rate 15 min after administration of nitroglycerin was registered, a significant decrease in pulse rate was measured in the placebo group.

In the present study, no prolonged uterine relaxation following administration of sublingual nitroglycerin was registered because following placental delivery immediately injection of oxytocin as well as removal of sublingual tablet helped the uterus to contract.

Neither the patients received nitroglycerin nor the patients received placebo develop post abortive bleeding affecting the general condition or requiring blood transfusion.

Conclusion

Sublingual nitroglycerin in association with oxytocin is a safe and effective drug in management of mid-trimesteric abortion retained placenta.

Corresponding author
Hosam M. Hemeda
Obstetrics and Gynaecology department, Faculty of Medicine, Ain-Shams University, Cairo. Egypt
Hosam1973md@gmail.com

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