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Nifedipine alone or combined with sildenafil citrate for management of threatened preterm labour: a randomised trial

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Objective To study the tocolytic action of nifedipine combined with sildenafil citrate (SC) and if the combination is superior to nifedipine alone in inhibiting threatened preterm labour (PTL).

Design Prospective randomised study.

Setting An Egyptian university hospital.

Population Women with threatened PTL who received either nifedipine with SC or nifedipine alone.

Methods Patients were randomly allocated to receive either (1) nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 6–8 hours at the same time as vaginal administration of SC (25 mg at 8-hourly intervals) or (2) nifedipine alone. Medications were continued for 48–72 hours.

Main outcome measures The percentage of women who remained undelivered during hospitalisation.

Results From January 2015 to November 2016, 239 women were randomised. The baseline characteristics of participants were similar. Nifedipine combined with SC was associated with

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more women remaining undelivered (81.8% versus 68.6%; *P* = 0.018) during hospitalisation. Regarding secondary outcomes, the addition of SC was also associated with fewer deliveries within 7 days of admission (9.1% versus 20.3%; *P* = 0.014), prolonged latency (29 versus 7 days; *P* = 0.002), fewer admissions to neonatal intensive care unit (31.4% versus 44.1%; *P* = 0.043), fewer very preterm deliveries (from 28 weeks to <32 weeks, 20.7% versus 38.1%; *P* = 0.043) and increased neonatal birth weight (1900 g versus 1500 g; *P* = 0.018).

Conclusions Vaginal SC combined with nifedipine is an effective option for tocolytic therapy during threatened preterm labour.

Funding No funding was received for this study.

Keywords Nifedipine, prematurity, sildenafil citrate, threatened preterm labour, tocolytic therapy.

Clinical trial registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT02337881.

Tweetable abstract: Vaginal SC enhances the tocolytic effect of nifedipine.

Introduction

Preterm labour (PTL) is any delivery after 20 weeks and before the completion of 37 weeks' gestation. Despite attempts aimed to reduce its incidence, statistics for 2010 showed that 14.9 million neonates were born preterm and of these 1.6 million were born very preterm (<32 weeks' gestation).[1] Accordingly, it is crucial to develop an appropriate approach for management of threatened PTL.

A previous preterm birth is the strongest risk factor associated with PTL, with a relative risk (RR) of 6.0 (95% CI 4.1–8.8) if the preterm birth was at <32 weeksand RR 4.8 (95% CI 3.9–6.0) if birth was between 32 and 36 weeks.[2] Other conditions that may increase a woman's individual risk include infection, uteroplacental ischaemia or haemorrhage, and uterine overdistension.[3]

Tocolytic therapy is used to postpone delivery for 24–48 hours to allow enough time for administration of corticosteroids to reduce the incidence and severity of respiratory morbidity and to arrange *in utero* transfer to a centre with proper neonatal intensive care unit (NICU)

facilities.[4] To date, there are no other interventions that have proven beneficial to the offspring.

Calcium channel blockers such as nifedipine reduce muscle contractility by decreasing calcium influx into cells. In one meta-analysis,[5] nifedipine was more effective and safer than ritodrine, while another meta-analysis[6] recommended it as the drug of choice for threatened PTL.

Sildenafil citrate (SC) is a selective inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase (PDE)-5. SC enhances smooth muscle relaxation by preventing degradation of the second messenger cGMP by phosphodiesterase. The relaxant action of cGMP in smooth muscle, through its downstream effector the enzyme protein kinase G, results in reduced intracellular calcium levels and a reduced sensitivity of the contractile elements to calcium.[7]

The human myometrium expresses several ion channels, the most abundant of which appears to be a large-conductance calcium-activated potassium channel (BKCa) which is pivotal in the control of uterine excitability, principally as a result of its direct association with intracellular calcium levels.[8] Moreover, BKCa channels have been implicated directly or indirectly in the actions of SC.

To date, no studies have explored the tocolytic effect of a combination of nifedipine and SC for threatened PTL. Our aim was to identify if this combination has a superior effect to nifedipine alone in terms of inhibiting threatened PTL and improving perinatal outcomes.

Methods

This was a randomised study approved by the ethics committee of the Menoufia University Hospitals, Shebin El-Kom, Egypt (OB/GYN protocols November 2014). The study was also registered at ClinicalTrials.gov (https://clinicaltrials.gov/) as NCT02337881. All participants provided their consent. The CONSORT guidelines were observed and completed. The GRIPP-SF (Guidance for Reporting Involvement of Patients and the Public) checklist was also followed to improve the quality, consistency and transparency of PPI reporting, and to ensure that PPI practice was based on the best evidence.

Recruitment started on 28 January 2015 and ended in November 2016 for cases of threatened PTL with a singleton pregnancy between 24 and 34 weeks' gestation, irrespective of whether or not the patient had a previous history of PTL. Cases included those presenting at the outpatient clinic or emergency room and those referred from other hospitals.

PTL was defined based on contraction frequency (persistence of at least two symptomatic uterine contractions within a 10-minute period during 60 minutes' observation) and cervical changes (cervical dilation between 0 and 3 cm for nulliparous and between 1 and 3 cm for multiparous, with cervical effacement less than 50%).[9]

Exclusion criteria were: multiple pregnancy, advanced cervical dilatation (>4 cm) with or without membranes bulging into the vagina, ruptured fetal membranes, suspected chorioamnionitis (unexplained fetal tachycardia or maternal temperature >38°C), contraindication for nifedipine and/or SC therapy, a major chronic medical disorder (such as chronic hypertension, chronic renal disease and pre-gestational diabetes mellitus, as these conditions would increase the risk of PTL and potentially confound the primary study outcome) and general contraindications to tocolytic therapy.

Women were randomly assigned in a 1:1 ratio to two study groups using a computerized random number table generator to obtain a trial sequence which was hidden in sealed numbered opaque envelopes prepared by the medical research officer in the hospital. Each envelope contained an assignment for a single patient. The statistician generated the random allocation sequence, and the investigators enrolled the participants. Patients in each group were masked regarding the management of threatened PTL in the other group but physicians were not.

All patients had an ultrasound examination prior to randomization to confirm gestational age. Cervical assessment by transvaginal ultrasound was also performed as a screening tool to determine the likelihood of birth within 48 hours of admission.[10] Dexamethasone in a total dose of 24 mg was given to all patients unless administered previously.

Patients were randomly allocated to receive either (1) nifedipine 20 mg orally (stat dose), followed by 10 mg orally every 6–8 hours at the same time as vaginal administration of SC (25 mg at 8-hourly intervals) or (2) nifedipine alone. Medications continued for 48–72 hours. No funding was received for this study.

During therapy, maternal (pulse rate, blood pressure, uterine contractions) and fetal (heart rate) monitoring was performed every 15–30 minutes during the first 4 hours following the start of therapy, then every 4 hours during the rest of the treatment. Patients in both groups whose contractions stopped were observed for an additional 24 hours to detect if contractions appeared again; if they remained stable they were discharged and asked to come for follow-up after 1 week. All discharged patients were offered prophylactic vaginal progesterone (Cycologest 400 mg; Actavis, Ireland and NJ, USA) to prevent recurrent PTL.[10] In addition to progesterone treatment, all patients were instructed to undergo more periods of bed rest

and also educated about symptoms of PTL. The provided antenatal care continued at 2-weekly intervals until delivery. At delivery, all data regarding labour, along with maternal and neonatal complications, were recorded.

Analysis was by intention to treat. Before discharge, the primary outcome was assessed based on the proportion of women remaining undelivered during the whole period of hospitalisation. Treatment failure was considered in participants who delivered during this period.

The antenatal visits and delivery notes were reviewed to get the secondary outcomes which addressed the core outcomes for prevention of PTL.[11] Four outcomes were related to the pregnant women: (1) harm to the mother from intervention, (2) maternal infection or inflammation, (3) prelabour rupture of membranes, and (4) maternal mortality. Eight outcomes related to newborns: (1) gestational age at birth according to standard subcategories (moderate to late preterm, gestation from 32 weeks + 0 days to <37 weeks + 0 days; very preterm, gestation from 28 weeks + 0 days to <32 weeks + 0 days; extremely preterm, gestation from <28 weeks + 0 days gestation),[12] (2) birth weight, (3) respiratory morbidity, (4) gastrointestinal morbidity, (5) infection (neonatal sepsis), (6) early neurodevelopmental morbidity (within 1 month of delivery), (7) harm to the neonate from intervention, and (8) perinatal mortality. Others were admission to the NICU, latency (time in days from randomisation until delivery) and any adverse drug effects.

For statistical purposes, Leyell et al.[13] found that PTL was prevented by nifedipine within 48 hours in 72% of cases. However, there are no literature reports on the use of SC either alone or in combination to prevent threatened PTL. We assumed an anticipated increase of 15% in the rate of reduction of PTL with the addition of SC to nifedipine, increasing the rate of prevention of PTL to 87%; accordingly, at a study power of 80% and two-tailed alpha of 0.05 a total sample size of 227 women is required considering a possible dropout rate of 10% of cases.

Statistical analysis was done using SPSS version 20 (IBM, Armonk, NY, USA). The qualitative data were expressed as percentages (%), while the quantitative data were examined using the Kolmogorov–Smirnov test to detect whether the data were normally distributed; if the data were normally distributed they were expressed as mean ± SD with Student's *t*-test being used for comparison; non-normally distributed data were expressed as

median (range) and the Mann–Whitney test was used for their comparison. A chi-square test or Fisher's exact test was used to test for differences in qualitative data. *P*-values < 0.05 were considered as significant.

Results

From January 2015 to November 2016, 239 women were randomised: 121 received nifedipine and SC while 118 received nifedipine alone; 226 of these completed their follow-up (94.6%). Analysis was by intention to treat. The randomisation, treatment and follow-up of participants are shown in Figure 1.

The baseline characteristics are shown in Table 1. No significant difference was observed between groups with regard to the assessed parameters.

The primary outcomes are shown in Table 2. The nifedipine–SC combination was associated with more women remaining undelivered (81.8% versus 68.6%; $P = 0.018$) during hospitalisation, fewer deliveries within 7 days of admission (9.1% versus 20.3%; $P = 0.014$) and prolonged latency (29.0 versus 7 days; $P = 0.002$).

The secondary maternal and offspring outcomes are shown in Table 3. Addition of SC was associated with fewer admissions to NICU (31.4% versus 44.1%; $P = 0.043$), fewer deliveries among the very preterm (from 28 weeks to <32 weeks, 20.7% versus 38.1%; $P = 0.003$) and increased neonatal birth weight (1900 g versus 1500 g; $P = 0.018$).

In terms of maternal adverse events, the nifedipine–SC group reported mild symptoms (24 patients, 19.8%) such as headache, facial flushing, nasal congestion and dyspepsia. These adverse events were also reported at similar rates in the nifedipine-alone group (23 patients, 19.5%). All adverse events were self-limited and managed conservatively. Both treatment groups reported no harm from intervention either on the maternal or the fetal side.

Discussion

Main findings

Our study has shown the tocolytic effect of a combination of nifedipine and SC to be superior to that of nifedipine alone in terms of inhibiting threatened PTL and improving perinatal outcomes, which appeared as fewer deliveries during hospitalisation or within 7 days after it, prolonged latency, reduction in total NICU admissions and deliveries among the very preterm with improvement in neonatal birth weight.

The current information is crucial for determining the possible role of SC in threatened PTL. In addition, in this study the median prolongation of pregnancy among the nifedipine-alone

group was 7 days, in line with the results of previously published larger studies: for example, in the APOSTEL study mean prolongation after nifedipine was only 7 days following threatened PTL.

Strengths and limitations

The strengths of our study were: (1) a well-designed randomised trial with adequate power calculations; (2) SC was tested at the usual doses used in previous studies to clinically confirm the hypothesis; (3) participants' outcomes were tracked until delivery to ensure the effect of implementation; (4) cervical status was taken at baseline; and (5) the outcomes were subdivided into primary and secondary and defined according to the CROWN initiative for comparison and combination in any meta-analysis. However, the following negative aspects could still be detected: (1) lack of blinding is a major risk of bias – physicians might discharge patients earlier or show other subtle changes in management if they are aware of group assignment, but objective outcomes are unlikely to be influenced by a lack of blinding; (2) the aetiology of premature uterine contractions (infection/inflammation?) was not considered before randomization; (3) SC was only used in combination with nifedipine so testing the effect of SC alone on threatened PTL was not done; (4) only one dose regimen was used although comparing the effect of different regimens may give different results; (5) the trial was not placebo-controlled; (6) maternal serum SC concentration was not measured; (7) obviously all or some of the patients had progesterone therapy to prevent PTL; (8) we were unable to determine the efficacy of this new combination for twins or preterm premature rupture of membranes due to their exclusion.

Interpretation

An ideal tocolytic agent should be easily administered, safe, specific to the myometrium, well tolerated and rapidly absorbed, with few adverse effects.[6] Nifedipine fulfilled most of these criteria so it was recommended as a first-line tocolytic therapy. Most of the previous criteria are also fulfilled by SC so it may have a possible therapeutic rule in threatened PTL.

In the human myometrium, the NO-cGMP pathway (the target for SC) has an important role in maintaining uterine homeostasis through its relaxing effect. Therefore, by increasing cGMP levels SC promotes the relaxation of uterine muscles.[14] However, this mechanism may not be very evident during pregnancy because the mediator (protein kinase G) which is responsible for the increase in cGMP appears to show decreased levels and reduced activity due to pregnancy itself.[15] This motivated Buxton[16] to study the role of NO, cGMP and oxytocin in uterine contractions and relaxations through a human pregnant myometrial cell

culture model, and in this regard intracellular calcium was found to be important in regulating the accumulation of cGMP in the myometrium.

Chiossi and colleagues[17] also tested the hypothesis that SC may potentiate the tocolytic effect of nifedipine by developing an *in vitro* model of myometrial biopsies from full term non-labouring women who were scheduled for caesarean section, and they concluded that SC, by virtue of its ability to reduce the intracellular calcium concentration, can augment the myometrial relaxing effect of nifedipine. Although these authors confirmed the potentiating efficacy of nifedipine if combined with SC, their model was *in vitro* with limitations in extrapolating from *in vitro* experiments to the *in vivo* situation during clinical application.

For a better understanding of the role of SC in myometrial smooth muscles, Khan et al.[18] found that relaxation occurred independently of cGMP, so they suggested that the effect of the drug on other myometrial ion channels is likely to play a role. Potassium channels could mediate this relaxation, as evident by the prolonged down-stroke of myometrial contractility when a model with blocked potassium currents was used. Although these authors did not test the effect of SC on calcium channels, they suggested that it had a role. The main difference between these findings and our study was that they tested SC on non-labouring myometrium after it was evoked by oxytocin while we used the drug after uterine contractions had begun spontaneously; the contribution of potassium channels could be different in each case. Again, they tested SC in very high concentrations that might have serious effects, especially on the cardiovascular system,[19] if used *in vivo*, while we used it in therapeutic doses.

The optimal dose of SC in threatened PTL has yet to be determined. The usual dosage is three times daily based on maximum median plasma concentrations reached within 60 min and a half-life of 4 hours,[20] but in pregnancy higher doses may be needed to reach a therapeutic plasma concentration as a result of altered plasma volume and pH.[21] This trial preferred the vaginal route for administration of SC because of its efficacy and safety with fewer adverse systemic events[22] and to limit the concern regarding the feto-maternal unit.[21] We selected the dose of SC to use in this study from pharmacokinetic data reported in a previous study.[23]

Regarding the safety of SC, although no deleterious effects were seen among babies after delivery there was no long term follow-up. Animal studies showed no fetotoxic or teratogenic effects for the drug even when used in very high doses,[24] and 3 years' follow-up in human showed no effect on the overall development of the babies.[25] Furthermore, as the drug would be administered in the third trimester, the risk of gross anomalies is over and the benefits outweigh the risks.

Conclusion

Using evidence-based practices to improve efficacy while maintaining quality, our study offers hope that the combination of SC with nifedipine appears to be superior to nifedipine alone in preventing threatened PTL. Larger studies with different dosage regimens, probably multicentre, are needed to confirm our findings and gain a better understanding of the mechanism of action of this novel therapeutic intervention.

Disclosure of interests

None declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

MAM, TMS and SEl-k developed the hypothesis. TMS collected the data and was involved in the care of the women. MAM was primarily responsible for writing the manuscript. SEl-k performed the analyses. All authors contributed to the interpretation of the data and manuscript preparation.

Details of ethics approval This study has been approved by the ethics committee of the Menoufia University Hospitals, Shebin El-Kom, Egypt (OB/GYN protocols, November 2014). The study was also registered at ClinicalTrials.gov, (https://www.clinicaltrials.gov) **NCT02337881**

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Figure legends:

Figure 1. The randomisation, treatment, follow-up and outcomes of participants.

Table 1. The baseline characteristics of participants

	Nifedipine–SC group (n = 121)	Nifedipine-only group (n = 118)	P-value	Odds ratio (95% CI)
Maternal age (years)	29 (20–41)	29 (19–38)	0.91*	–
Parity				
Nulliparous	13 (10.7)	13 (11.0)	0.95†	1.03 (0.46–2.32)
Multiparous	108 (89.3)	105 (89.0)		
Body mass index (kg/m^2)	26 (19–39)	25 (20–36)	0.19*	–
History of PTL	23 (19.0)	26 (22.0)	0.56†	–
GA at randomisation (days)	210 (168–235)	207 (170–235)	0.68*	–
Use of nifedipine or progesterone before randomization	11 (9.1)	15 (12.7)	0.37†	1.46 (0.64–3.32)
Cervical length by TVUS (mm)	25 (15–35)	25 (16–34)	0.89*	–
Total days of hospital admission	3 (2–4)	3 (2–4)	0.86*	–
Total dose of nifedipine given (mg)	120 (80–140)	120 (80–140)	0.73*	–
Compliance with progesterone therapy after discharge	78 (64.4)	79 (66.9)	0.68†	1.12 (0.75–1.60)

GA, gestational age; PTL, preterm labour; TVUS, transvaginal ultrasound.
Data are expressed either as median (range) or number (%).
Statistical tests: *Mann–Whitney test; †chi-square test.

Table 2. Primary outcomes according to treatment

	Nifedipine–SC group (*n* = 121)	Nifedipine-only group (*n* = 118)	*P*-value	Odds ratio (95% CI)
Delivery within 24 hours of admission	6 (5.0)	8 (6.8)	0.55*	1.39 (0.47–4.15)
Delivery within 48 hours of admission	8 (6.6)	11 (9.3)	0.44*	1.45 (0.56–3.75)
Delivery within 72 hours of admission	8 (6.6)	18 (15.3)	0.032*	2.54 (1.06–6.10)
Cases remain undelivered during hospitalisation	99 (81.8)	81 (68.6)	0.018*	0.49 (0.27–0.89)
Delivery after discharge (≤7 days from admission)	11 (9.1)	24 (20.3)	0.014*	2.55 (1.18–5.49)
Latency (time in days from randomisation until delivery)	29 (1-76)	7 (1-68)	0.002†	–

Data expressed as: number (%) or median (range).
Statistical tests: *chi-square test; †Mann–Whitney test

Table 3. Secondary maternal and offspring outcomes according to treatment

	Nifedipine–SC group (*n* = 121)	Nifedipine-only group (*n* = 118)	*P*-value	Odds ratio (95% CI)
Prelabour rupture of membranes	22 (18.2)	18 (15.3)	0.54*	0.81 (0.41–1.60)
Harm to mother from intervention	0	0	–	–
Maternal infection	1 (0.8)	0	0.32*	–
Maternal mortality	0	0	–	–
Admission to NICU	38 (31.4)	52 (44.1)	0.043*	1.72 (1.01-2.92)
Gestational age at delivery:	6 (5.0)	11 (7.6)		
Extremely preterm (<28 weeks)	25 (20.7)	45 (38.1)	0.39*	1.58 (0.55–4.60)
Very preterm (28 to <32 weeks)	56 (46.3)	44 (37.3)	0.003*	2.37 (1.33–4.21)
Moderate to late preterm (32 to <37 weeks)			0.16*	0.69 (0.41–1.16)
Neonatal birth weight (g)	1900 (600-3100)	1500 (650-3700)	0.018†	–
Respiratory morbidity	35 (28.9)	51 (43.2)	0.021*	1.87 (1.09–3.19)
Gastrointestinal morbidity	6 (5.0)	9 (7.6)	0.039*	1.58 (0.54–4.95)
Early neurodevelopmental morbidity (within 1 month of delivery)	16 (13.2)	11 (9.3)	0.34*	0.68 (0.29–1.52)
Neonatal infection	15 (12.4)	16 (13.6)	0.79*	1.11 (0.52–2.36)
Perinatal death	7 (5.8)	12 (10.2)	0.21*	1.8 (0.70–4.86)
Harm to offspring from intervention	0	0	------	----------

NICU, neonatal intensive care unit.
Data are expressed either as number (%) or median (range).
Statistical tests: *chi-square test; †Mann–Whitney test.

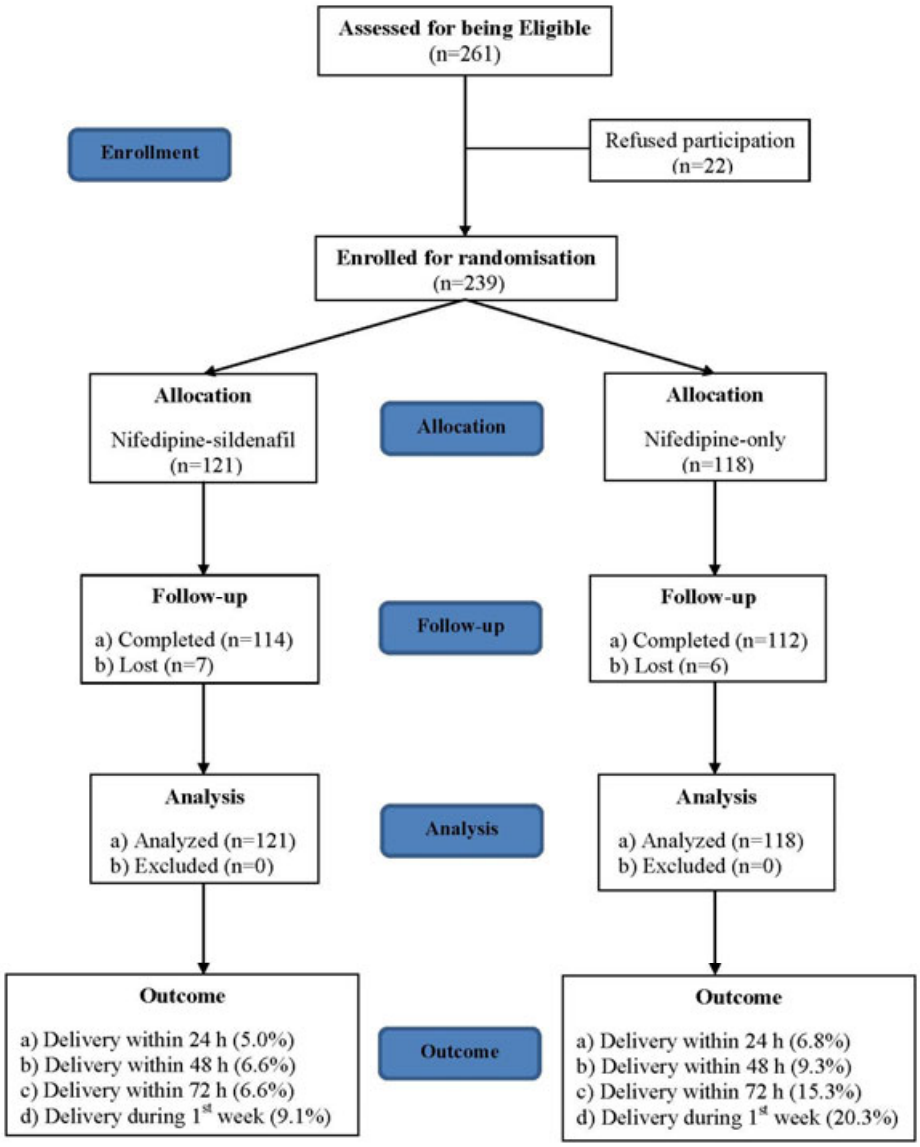

Figure (1): The randomisation, treatment, follow-up, and outcomes of participants.