International Journal of Gynecology and Obstetrics xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

journal homepage: www.elsevier.com/locate/ijgo

www.figo.org

CLINICAL ARTICLE

Intra-amniotic instillation of surfactants for the prevention of neonatal respiratory distress syndrome following preterm delivery

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ARTICLE INFO

Article history:
Received 15 December 2015
Received in revised form 22 March 2016
Accepted 22 July 2016

Keywords:
Intra-amniotic
Preterm birth
Respiratory distress syndrome
Surfactant

ABSTRACT

Objective: To assess the efficacy of intra-amniotic administration of surfactants in reducing the incidence and severity of respiratory distress syndrome (RDS), and the need for postnatal endotracheal surfactant during preterm delivery. *Methods:* A prospective pilot study enrolled pregnant women at 28–34 weeks of pregnancy between July 1, 2013 and December 31, 2014 who were randomly assigned in a 1:1 ratio to a control group or to receive intra-amniotic surfactant (3 mL) administered under ultrasonography guidance within 2–8 hours of expected delivery. The primary outcomes, the incidence and severity of RDS, and the need for postnatal surfactants, were analyzed on an intention-to-treat basis. *Results:* The study enrolled 20 patients to each group. The incidence of RDS did not differ between the two groups ($P = 0.110$). Severe RDS was more common in the control group ($P = 0.018$) and postnatal surfactants were required more frequently in the control group ($P = 0.02$). *Conclusion:* Intra-amniotic administration of surfactants reduced RDS severity and the need for postpartum endotracheal surfactants.

Clinical Trials Registry India: CTRI/2015/12/006399

1. Introduction

Respiratory distress syndrome (RDS) continues to be a leading cause of morbidity and mortality during preterm delivery [1–3]. Prenatal corticosteroids are required to prevent RDS; unfortunately, these only take effect 48 hours after administration. Endotracheal surfactants are administered to neonates with features of RDS but they can lead to hypoxia, bradycardia, pneumonia, and long-term sequelae [1,3]. It has been hypothesized that the prenatal administration of surfactants could prevent the onset of RDS.

Peripartum administration of surfactants, including pharyngeal instillation before the first breath and administration via laryngeal mask, could obviate the need of endotracheal surfactants [1,3]. However, questions have been raised regarding the practical feasibility of pharyngeal instillation of surfactants and the laryngeal-mask method has not been proven to be efficacious in the prevention and treatment of RDS [4]. Prepartum intra-amniotic instillation of surfactants prior to preterm delivery could be a promising option in preventing RDS and initial animal studies have demonstrated the efficacy and feasibility of intra-amniotic surfactants in preventing RDS during preterm delivery [5,6]. There are very few data from humans available for this method in the literature [7–9]. Consequently, the aim of the present study was to assess the effects of intra-amniotic surfactants on the incidence and severity of RDS during preterm delivery, and on the need for postnatal endotracheal surfactant treatment.

2. Materials and methods

The present prospective, randomized pilot study was conducted at the Department of Obstetrics and Gynecology at the All India Institute of Medical Sciences, New Delhi, India, between July 1, 2013 and December 31, 2014. Patients attending the study institution experiencing preterm labor or for a preterm cesarean delivery were recruited. Patients aged 22–40 years at 28–34 weeks of pregnancy who were experiencing active labor (labor pains and cervical dilatation ≥3 cm) or were scheduled to undergo an emergency cesarean delivery were eligible for recruitment. Patients were excluded if they had preterm premature rupture of membranes, chorioamnionitis, or congenital fetal anomalies. The study was approved by the All India Institute of Medical Sciences ethics committee and all participants provided written informed consent to participate.

Participants were randomized using a random number table in a 1:1 ratio into two groups using Random Allocation Software version 2 [10]; participants in the study group received intra-amniotic surfactants and the other group was a control group. Both investigators and participants were unmasked to the group allocations.

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http://dx.doi.org/10.1016/j.ijgo.2016.03.039

Participants in the study group received intra-amniotic surfactants within 2–8 hours of expected delivery. Prior to surfactant instillation, a 3-mL amniotic-fluid sample was aspirated to assess fetal lung status using the foam stability test; if a positive foam stability test result was recorded, the participant was excluded from the study. Surfactant administration was performed using ultrasonography guidance with a 22-G spinal needle. An appropriate amniotic fluid pocket was selected, preferably near the fetal face, to facilitate entry of surfactant into the fetal respiratory tract; 3 mL of natural bovine lipid extract surfactant (Neosurf; Cipla Inc, Mumbai, India) was administered. According to the routine protocol at the study institution, prenatal corticosteroids were administered to participants in both groups.

Following delivery, neonatal-outcome parameters were recorded by the pediatric team. The primary outcomes were the incidence of RDS, the incidence of severe RDS, and the need for postnatal endotracheal surfactants. Severe RDS was assessed using the Silverman–Andersen scoring system [11], an objective 10-point scale for assessing RDS in preterm neonates; a score of 0 indicated no RDS while a score of 10 indicated the most severe form of RDS. Silverman–Andersen scores above seven imply impending respiratory failure [11] and in the present study, scores of at least seven were considered to indicate severe RDS. RDS was diagnosed and Silverman–Andersen scores were assessed within the first 24 hours of delivery. The secondary outcomes were Apgar score, the use of and duration of continuous positive airway pressure (CPAP), the fractional inspiration of O_2 (FiO_2) during CPAP, and the need for mechanical ventilation.

In addition to the primary analyses, outcomes were also considered using two subgroups (28–31 weeks and 31^{+1}–34 weeks, coded A and B, respectively) within each participant group (the study and control groups, coded 1 and 2, respectively). The outcomes were also compared based on the location of surfactant administration (either near to the fetal face or away from the face).

A sample size of 50 participants in each group was calculated to yield 80% power with 95% confidence; however, owing to the trial being a pilot study, a total target sample size of 20 patients in each group was selected.

Data analyses were performed by intention to treat using SPSS version 19 (IBM, Armonk, NY, USA). The χ^2 and Fisher exact tests were used for the analyses and $P < 0.05$ was considered statistically significant.

3. Results

Patient recruitment proceeded until 20 patients had been randomized to each of the two study groups (Fig. 1). The baseline data did not differ between the two groups (Table 1) and none of the participants reported any history of cigarette smoking. In the study group, the mean time interval between surfactant instillation and delivery was 177 ± 77 minutes (range 120–420 minutes). Across the complete study population, 36 (90%) participants underwent cesarean deliveries, with all 4 (10%) of the participants who underwent vaginal delivery originating from the control group. There was no statistically significant difference in the cesarean/vaginal delivery rate between the two groups ($P = 0.106$). The indications for cesarean deliveries are detailed in Table 2. The mean neonatal weight at delivery was comparable between the study and control groups (1295 ± 475 g [range 566–2195 g] vs 1300 ± 388 g [range 762–2052 g], respectively; $P = 0.970$).

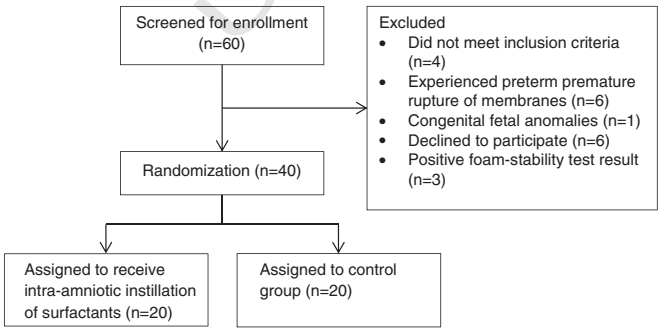

Fig. 1. Flow of participants through the study.

Table 1
Baseline demographics of study participants (n = 40).[a]

Variable	Study group (n = 20)	Control group (n = 20)	*P* value
Age, y	30.4 ± 5.8 (22–45)	27.8 ± 3.5 (23–35)	0.090
Parity	1.2 ± 1.1 (0–4)	1.3 ± 1.6 (0–6)	0.820
Duration of pregnancy at delivery, wk	31.9 ± 1.7 (28.1–34.0)	30.9 ± 2.0 (28.0–34.0)	0.110
Hemoglobin, g/L	113 ± 19 (80–145)	110 ± 14 (80–136)	0.500
Hypertension	13 (65)	10 (50)	0.337
Gestational diabetes mellitus	9 (45)	5 (25)	0.185
Thyroid disorder	7 (35)	3 (15)	0.273
Oligohydramnios	8 (40)	5 (25)	0.311
Intrauterine growth restriction	6 (30)	4 (20)	0.465

[a] Values are given as mean ± SD (range) or number (percentage), unless indicated otherwise.

There was no difference in the incidence of RDS between the two groups but the incidence of severe RDS and requiring postnatal endotracheal surfactants were higher in the control group (Table 3). Apgar scores at 1 minute and 5 minutes, the use and duration of CPAP, and the need for mechanical ventilation did not differ between the two study groups. The FiO_2 during CPAP was higher in the control group (Table 3).

Within the study group, 7 (35%) participants were at 28–31 weeks of pregnancy and 13 (65%) were at 31^{+1}–34 weeks of pregnancy; in the control group, there were 10 (50%) participants in each of these subgroups (Fig. 2). Among participants experiencing preterm labor at 28–31 weeks of pregnancy, the incidence of severe RDS was higher in the control group; a higher incidence of requiring postnatal endotracheal surfactants was also observed in the control group among participants experiencing preterm labor at 31^{+1}–34 weeks of pregnancy (Table 4).

Among the participants in the study group, the location of surfactant instillation was recorded as near the fetal face for 17 (85%) participants and away from the fetal face for 3 (15%) participants. There was no difference between the "near fetal face" subgroup and the "away from fetal face" subgroup in the incidence of RDS (7/17 [41%] vs 2/3 [67%]; $P = 0.566$), the incidence of severe RDS (0/17 vs 1/3 [33%]; $P = 0.150$), and the need for postnatal endotracheal surfactants (2/17 [12%] vs 1/3 [33%]; $P = 0.404$).

Among participants in the study group, no neonates had Silverman–Andersen scores of 10, compared with two neonates in the control group. Among the neonates who experienced mild RDS (Silverman–Andersen scores <7), all of them had scores of 3–6. The development of bronchopulmonary dysplasia was recorded for four neonates from each group. In the study group, there was one infant death (weight at delivery 566 g); this occurred at 50 days after delivery and was caused by late-onset neonatal sepsis, refractory shock, and cardiac arrest. This

Table 2
Indications for cesarean deliveries.[a] [b]

Indication	Study group (n = 20)	Control group (n = 16)	*P* value
Fetal Doppler anomaly	12 (60)	7 (44)	0.113
Non-reassuring fetal heart rate	4 (20)	3 (19)	>0.99
Poor biophysical profile	1 (5)	0	>0.99
Prepartum hemorrhage	0	2 (13)	0.231
Maternal indication	3 (15)	8 (50)	0.155

[a] Values are given as number (percentage) unless indicated otherwise.
[b] The difference in the cesarean delivery rate between the two groups was not significant ($P = 0.106$).

Please cite this article as: Agarwal N, et al, Intra-amniotic instillation of surfactants for the prevention of neonatal respiratory distress syndrome following preterm delivery, Int J Gynecol Obstet (2016), http://dx.doi.org/10.1016/j.ijgo.2016.03.039