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Original Article

Domperidone and maternal milk volume in mothers of premature newborns

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Abstract

Background Mothers of premature newborns often have difficulty giving adequate breast milk volume to their infants. Domperidone is an antagonist of peripheral dopamine receptors and believed to increase breast milk production. In Indonesia, no study has been done to date on the effect of domperidone on maternal milk production in mothers of premature newborns.

Objective To evaluate the effect of domperidone on milk production in mothers of premature newborns who failed to lactate.

Methods A randomized controlled trial was conducted from July to December 2012 in the Perinatology Unit, Haji Adam Malik Hospital, Medan. Mothers of premature newborns were given lactation counseling for 7 days in order to increase their milk production. Mothers who failed to lactate after that time were enrolled in the study. Fifty subjects were assigned to receive either domperidone or a placebo for 7 days. Milk volume was measured every 2 hours (from 7 am to 9 pm), in the 24 hours before starting therapy, and on the 7*th* and 10*th* days (the 10*th* day being 3 days after stopping therapy).

Results This study involved 25 mothers in the domperidone groups and 25 others in placebo group. After 7 days of therapy, mean breast milk volume was significantly higher in the domperidone group than in the placebo group [181.6 (SD 80.2) *vs.* 72.4 (SD 57.8) mL, respectively; 95%CI of differences 69.36 to 148.93; P=0.0001]. At day 10, breast milk production remained significantly higher in the domperidone group. Furthermore, in the domperidone group, no significant difference in mean breast milk volumes was noted between the 7th and 10th days (P=0.65).

Conclusion In mothers of premature newborns who failed to lactate, domperidone therapy for 7 days causes significantly higher milk production compared to placebo. **[Paediatr Indones. 2017:57:17-22. doi: 10.14238/pi57.1.2017.17-22]**.

Keywords: *domperidone; premature newborn; breast milk*

Low birth weight (LBW) and prematurity are the leading causes of perinatal death in Indonesian hospitals. In 2005, the percentage of live birth infants with low birth weight was 27.9% in Indonesia.[1] Breast milk is the best food for babies and preterm infants. Breastfeeding is beneficial for babies, mothers, families, communities, the environment, and countries. Breastfeeding is expected to decrease the mortality and morbidity of newborn preterm infants.[2] Generally, mothers who give birth to term infants produce sufficient milk in the first week after delivery. However, mothers of preterm babies often have inadequate milk production. Various strategies to increase milk production have been reported, such as relaxation techniques, use of mechanical devices, and medications.[3]

Domperidone is a peripheral dopamine receptor antagonist that is thought to work by blocking the

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inhibitory effects of dopamine-mediated prolactin secretion, thereby increasing milk production.[4,5] There was still a few study on domperidone effects to human milk production. In addition, there has been no study on the effects of domperidone on milk production in Indonesian mothers who gave birth to preterm babies.

We aimed to evaluate milk production in mothers who delivered preterm infants after administering domperidone. We also assessed for possible relationships between milk production and maternal age, gestational age, parity, method of delivery, and educational level.

Methods

A randomized double-blind controlled trial was conducted to assess the effect of domperidone (group A) compared to that of placebo (group B) on milk production in mothers who gave birth to preterm babies. Subjects were recruited from the Perinatology Unit, Haji Adam Malik Hospital, Medan from July to December 2012.

The inclusion criteria were mothers aged 20 to 30 years who gave birth to infants with gestational age < 37 weeks, as well as failure to lactate with little or no improvement in milk production after one week of lactation counseling, along with the baby receiving feeding through a nasogastric tube. Exclusion criteria were mothers who used medications that affect domperidone (e.g., antacids, cimetidin, ranitidine, famotidine, or nizatidine) or medications that interact with domperidone (e.g., haloperidol or lithium), mothers with mastitis, had undergone breast surgery, had heart problems, obesity, diabetes, or twins. Subjects were randomized into domperidone and placebo groups by randomization tables.

Prior to enrollment, mothers underwent ECG examinations to assess heart rhythm, followed by lactation counseling for 7 days in order to maximize breast milk production. If the counseling method failed, then the mothers were eligible to participate in the study. Domperidone was administered orally at a dose of 10 mg, 3 times per day for 7 days. Tablets were crushed, mixed with lactose, then put into capsules. Placebo was lactose powder alone in capsules. All subjects received 21 capsules to be taken 3 times daily for 7 days. A female health worker was employed to supervise the administration of medication and help subjects pump breast milk. Breast milk was collected using a double breast pump (*Medela* ®), for 15 minutes per pump cycle, done daily from 7:00 am to 9:00 pm, every 2 hours. The collected breast milk was measured by researchers and given to the preterm babies. The volume of breast milk counted each day for 1 week. Subjects noted their complaints during treatment, such as dry mouth, headache, insomnia, abdominal pain, diarrhea, nausea, or urinary retention. Breast milk volume was measured at 24 hours prior to the start of medication, 7 days after medication, and day 10 (3 days after stopping the medication). Failure to lactate was defined as decreased breast milk supply (more than 30% of maximum breast milk volume) and/or inability to produce an adequate amount of breast milk to meet the infant's daily nutritional needs.[4]

We used unpaired T-test to compare mean volumes of breast milk in the domperidone and placebo groups. The comparison of mean breast milk volumes on days 7 and 10 in both groups were analyzed by paired T-test. Multivariate analysis was used to determine the relationship between breast milk volume and maternal age, gestational age, number of children, method of delivery, and educational level. Data processing was done with *SPSS 15* software, and results were considered to be significant for P values <0.05 and 95% confidence intervals (CI). This study based on intention to treat analysis.

Subjects provided informed consent for participation. This study was approved by the Ethics Committee of the University of Sumatera Utara Medical School.

Results

At our hospital there were 107 preterm births from July to December 2012, of whom 64 mothers had inadequate breast milk volume. Twelve mothers were excluded because their infants were of gestational age > 37 weeks (4 mothers), they were aged > 30 years (3 mothers), they were obese with BMI > 30 kg/m2 (3 mothers), or they delivered twins (2 mothers). Fifty-two mothers who met the inclusion criteria underwent ECG examination to screen for cardiac arrhythmias; all had normal ECG results. These mothers underwent

a lactation counseling program for 7 days to learn to increase their breast milk production. Two infants died during treatment due to respiratory distress from hyaline membrane disease and sepsis. The remaining 50 mothers completed the lactation counseling program, but failed to lactate. These mothers were randomized into the domperidone or placebo groups, each consisting of 25 mothers. During the study, four mothers dropped out because their infants died, three from the placebo group and one from the domperidone group (**Figure 1**). The infants who died were diagnosed with respiratory distress due to hyaline membrane disease and sepsis.

Table 1 shows the characteristics of subjects. Mean maternal ages in the domperidone and placebo groups were 26 and 25 years, respectively. Mean number of children borne by mother in both groups was one, and mean gestational age in both groups was 31 weeks. More subjects in the domperidone group delivered vaginallly than by caesarean section, but in the placebo group, more subjects underwent caesarean section than vaginal delivery. Most mothers in both groups finished high school (48% and 52%, respectively) and 96% in both groups were housewives. Mean infant birth weights in the domperidone and placebo groups were 1,656 and 1,636 grams, respectively, while mean infant age at hospital admission for both groups was 5 days. Mean breast milk volume prior to therapy was 83.3 (SD 42.99) mL in the domperidone group and 66.6 (SD 49.84) mL in the placebo group.

Differences in breast milk volume between the domperidone and placebo groups on day 7 of treatment and day 10 (3 days after stopping treatment) are shown in **Table 2.** Unpaired T-test revealed that the domperidone group had significantly greater mean breast milk volume than the placebo group on both days (P=0.0001, for day 7 and day 10).

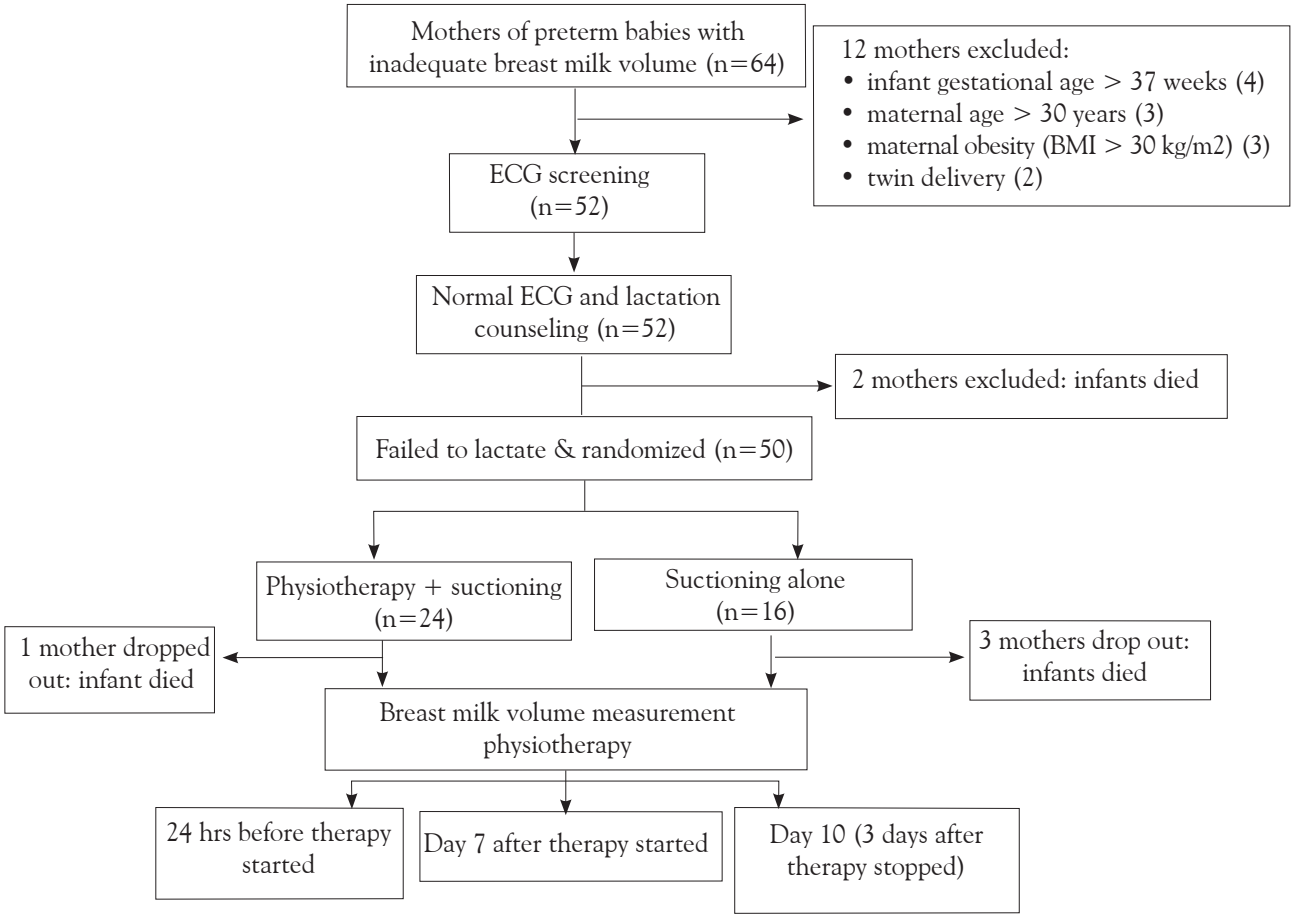

Figure 1. Study profile

Table 1. Baseline characteristics of subjects

Characteristics	Domperidone group (n=25)	Placebo group (n=25)
Mean maternal age (SD), years	26.8 (3.47)	25.7 (3.67)
Mean number of children born by mother (SD)	1.9 (0.83)	1.7 (0.9)
Method of delivery, n		
Vaginal	14	11
Cesarean section	11	14
Maternal education, n		
Primary school	8	7
Junior high school	4	5
Senior high school	12	13
Diploma	1	0
Scholar/master	0	0
Employment, n		
Government	0	0
Private sector	0	0
Enterpreneur	1	1
Farmer/fisherman	0	0
Housewife	24	24
Mean birth weight (SD), grams	1,656.8 (346.2)	1,636.8 (386.75)
Mean infant age (SD), days	5.6 (6.75)	4.8 (4.42)
Mean breast milk volume prior to therapy onset (SD), mL	83.3 (42.99)	66.6 (49.84)

Table 3 shows the comparison of mean breast milk volume on day 7 of treatment and day 10 in the domperidone group. Paired T-test revealed no significant differences in mean breast milk volume ($P>0.05$) between day 7 and day 10. In the placebo group, there were no significant differences in mean breast milk volume before treatment, day 7, and day 10 ($P>0.05$).

Multivariate linear regression analysis of number of children, maternal education, and type of therapy on day 7 of treatment showed that type of therapy could be used to predict breast milk volume on day 7 of treatment (correlation strength 0.623). The equation was breast milk volume = 72.46 + 109.14 (therapy type). Domperidone had a value of 1, while placebo was given a value of 0. ANOVA test revealed $P<0.05$, so we concluded that the equation was appropriate.

Table 3. Comparison of breast milk volume on days 7 and 10 in the domperidone group

Day of treatment	n	Mean breast milk volume (SD), mL	95% CI of differences	P value
Day 7	25	181.6 (80.26)	-8.67 to 13.64	0.65
Day 10	25	179.1 (82.4)		

None of our subjects complained of possible domperidone side effects, such as dry mouth, headache, abdominal pain, or tension in the breasts.

Discussion

In our study, the mean age of mothers who received domperidone was 26 years, with infants of 31 weeks mean gestational age. Characteristics of subjects in this study were similar to those in a 2006 Canadian study. A previous study assessed domperidone effects on breast milk production in subjects aged 28 years who gave birth vaginally to infants of 29 weeks gestation. They had only 16 subjects, whereas our study involved 50 subjects, and they did not assess the method of delivery, although Caesarean section is known to be a risk factor for lactogenesis delay.6 However, our study showed no difference in breast milk volume regarding method of delivery.

We found significantly increased breast milk production in the domperidone group on day 7 of treatment. Mean breast milk volume in the domperidone group was 181.6 (SD 80.2) mL *vs.* 72.4 (SD 57.8) mL in the placebo group (95%CI 69.36 to 148.93; $P < 0.0001$). This finding was consistent with a 2012 systematic review that assessed effects of domperidone on lactation insufficiency in women who gave birth to preterm and full-term infants. The results of three randomized, double-blind studies all showed significant increases in breast milk production after administration of domperidone. Data analysis showed significant increases of 75.36% (95%CI 55.42 to 95.3; $P=0.00001$) in daily breast milk production after taking domperidone compared to placebo. A limitation of this meta-analysis was that the three clinical trials had small

Table 2. Comparison of breast milk volume between the domperidone and placebo groups

Mean breast milk volume (SD), mL	Domperidone group	Placebo group	95% CI of differences	P value
Day of treatment				
Day 7	181.6 (80.26)	72.46 (57.84)	69.36 to 148.93	0.0001
Day 10	179.12 (82.4)	69.32 (51.74)	70.67 to 148.93	0.0001

sample sizes (17, 16, and 45 subjects each). Clinical trials with small sample sizes may be subject to random error.[7] A large, multi-center study was conducted in Toronto in 2012 as a randomized, double-blind clinical trial of 560 mothers who gave birth to preterm babies. This study was still running as of the writing of this paper, as a protocol study.[8]

Domperidone increases breast milk production by working as dopamine receptor antagonist in the striata area, acting to inhibit the anterior pituitary dopamine receptor or the tuberoinfundibular system. Domperidone blocks the inhibitory effects of dopamine-mediated prolactin secretion in the anterior pituitary, resulting in increased serum prolactin levels and thus, breast milk production.[9,10,11] The recommended dose of domperidone as a galactogogue is 10 mg orally, administered 3 times per day for 1 to 2 weeks.[7,12] However, there is no definitive guideline on the domperidone dose that will increase breast milk production. A randomized clinical trial with double-blind design was conducted in Australia on 6 mothers of preterm infants. Mothers received domperidone at doses of 30 and 60 mg/day. Two-thirds of subjects showed significant increases in breast milk production and serum prolactin. The increase in breast milk production occurred when the dose was increased from 30 to 60 mg, although the amount of domperidone in breast milk was quite low and has minimal risk to breastfed babies.[10] Another Canadian study in 2012, compared two doses of domperidone to increase breast milk production and found that an increase of domperidone dose from 10 mg orally 3 times daily to 20 mg increased breast milk production, similar to previous studies.[8] However, Health Canada issued a warning about domperidone doses exceeding 30 mg/day.[13] We used a minimum dose of 10 mg orally 3 times per day as no Indonesian studies have assessed the optimum dose of domperidone to increase breast milk production. Moreover, this dose was chosen to avoid possible side effects, especially arrhythmia.

The optimal duration of domperidone treatment to increase breast milk production is unknown. Previous studies used domperidone for 7, 10, and 14 days as well as 4 weeks.[2,8,14,15] All of these studies showed increased breast milk production after administering domperidone. We administered domperidone for 7 days due to difficulty subject compliance for taking medication and pumping breast milk every 2 hours each day. Before the study began, subjects underwent lactation counseling for 7 days and were asked to pump their breast milk every 2 hours. Hence, we required only 7 days of treatment in order to improve subject adherence to the regimen.

Breast milk volume at day 7 of treatment was not significantly different to that at 3 days after stopping the treatment [181.6 (SD 80.26) mL *vs.* 179.1 (SD 82.4) mL, respectively (P=0.65)]. This finding suggests that breast milk production remained increased 3 days after stopping treatment.

Factors that were assessed for their effect on breast milk volume in this study were number of children borne by mother, maternal education, and type of medication. Multivariate analysis showed that type of medication with a strength of correlation of 0.623 could be used to predict breast milk volume on day 7 of treatment.

Subjects had no complaints about side effects such as dry mouth, headache, abdominal pain, or tension in the breasts. Arrhythmia is a serious side effect that can occur. We assessed subjects for arrhythmias by ECG examination and found no abnormalities in all 50 subjects. With regards to possible side effects, the *Food and Drug Administration* (FDA) in 2004 suggested that breastfeeding mothers not take domperidone due to the risk of cardiac arrhythmias and sudden death. These fates were observed in cancer patients with low potassium levels who received high-dose intravenous domperidone with chemotherapy.16 However, the FDA-issued warning was somewhat of an overreaction, because the subjects who received domperidone had comorbidities, were undergoing chemotherapy, and had severe hypokalemia. In addition, the bioavailability of oral domperidone is only 13 to 17% and peak levels of domperidone at doses of 10 mg orally are only about 1/30 that of administration via the parenteral route.[13]

Limitations of the study were that we did not measure serum prolactin or domperidone levels in breast milk, due to lack of measurement tools and facilities in Haji Adam Malik Hospital. We also did not assess the optimum dose and duration of domperidone administration to maintain breast milk production. Breast milk composition such as protein, glucose, and lipid levels were also not determined in the study.

In conclusion, domperidone significantly increases breast milk production compared to placebo

in mothers who gave birth to preterm babies. In the domperidone group, mean breast milk volume 3 days after stopping treatment is not significantly different from mean breast milk volume at day 7 of treatment. No side effects associated with domperidone treatment is found in our subjects.

Conflict of interest

None declared.

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