EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 6
90-94
Year: 2019

EFFECT OF ANTENATAL DOMPERIDONE VERSUS PLACEBO ON BREAST MILK PRODUCTION BETWEEN MOTHERS IN ACTIVE LABOR

Rauniyar H. K.[1], MD, Sah R. P.[2], MS, Singh A. K.[1], MD and Sah R. G.*[3], PhD

[1]Deapertment of Paediatric, BPKIHS, Dharan.
[1]Department of Pediatrics, Section of Newborn Medicine, Cagayan Valley Medical Center.
[2]Department of Surgery, Paediatric Surgery Division, BPKIHS, Dharan.
[3]Department of Clinical Neurosciences, Foothills Medical Centre, University of Calgary, Canada.

***Corresponding Author: Dr. Sah R. G.**
Department of Clinical Neurosciences, Foothills Medical Centre, University of Calgary, Canada.

Article Received on 03/04/2019 **Article Revised on 24/04/2019** **Article Accepted on 14/05/2019**

ABSTRACT
This randomized double blind placebo controlled Phase II clinical trial study aims to determine the effectiveness of antenatal domperidone in increasing breast milk volume among thirty enrolled mothers in labor. The treatment group was given 10 mg domperidone tablets while the control group received identical placebo tablets to be taken thrice a day for three days postpartum. Mothers breastfed their infants per demand and also manually expressed their breast milk on the 18th, 36th and 72nd hours post-partum and milk volume was measured. The domperidone and the control groups were comparable with regards to demographic, socioeconomic and clinical profile. The mean volume of milk and (95% Confidence Interval of the Mean) at 18th hours was 1.61 ml (-2.14 ml to 5.36 ml) was increased to 6.46 ml (-4.3 ml to17 ml) at 36th hours was further increased to 12.39 (-10.99 ml to 35.77 ml) at 72 hours in domperidone group. Whereas, in the placebo group the mean volume of milk and (95% Confidence Interval of the Mean) at 18th hours was 0.26 ml (-0.56 ml to 1.10 ml); at 36th hours was 2.40 ml (-4.45 ml to 9.28 ml) and was 4.89 (-7.55 ml to 17.34 ml) at 72 hours. The volumes of breast milk on the 18^{th,} 36th, and 72nd hours postpartum were significantly higher between the domperidone group compared to the control ($p<0.05$). In conclusion, antepartum domperidone is an effective drug in increasing breast milk production during active labor.

KEYWORDS: Domperidone, Placebo, Breast milk, Active Labor, clinical trial.

INTRODUCTION
Exclusive breastfeeding has been recognized as the major strategy to decrease neonatal mortality and morbidity, further it is proven to be effective and cost-efficient. With 10 million deaths of infants and young children globally, breastfeeding as a solution saves 1.3 million lives annually.[1] In Philippines out of almost 7 million children (below 5 years old), 87% were ever breastfed. This figure however includes infants whose breastfeeding may have lasted for only 1 hour, 1 day a week only. In fact, nearly 3.4 million children (49%) were given liquid or food other than the breast milk within 3 days after being born. For children below 3 years old at the time of survey, barely 6% were exclusively breastfed. Bottle-feeding was common for almost half of these children.[3]

The literature reports the risk of death due to infection increases with longer delay in breastfeeding initiation.[1] Partial breastfeeding is also associated with a 5.7 fold increased risk of death due to infection.[1] In Philippines, the average duration of exclusive breastfeeding among mothers is only 24 days; with the oft-spoken reason by mothers being inadequacy of breast milk let down.[2] One possible solution is the use of domperidone; a dopaminergic blocking agent which has been reported to be a potent lactagogue by increasing prolactin levels. Till date, no clinical trials in the Philippines have been published regarding the use of a synthetic lactagogue like domperidone in improving breast milk let down.

The aim of this study was to determine the efficacy of antenatal domperidone in increasing the volume of breast milk production between mothers in active compared to mothers in active labor given placebo.

One significance important of this study notwithstanding from evaluating initially the potential of domperidone as a lactagogue in a Phase II Clinical Study is that a positive outcome will be a foundation for a large sample size study (Phase III with a bigger sample size in different hospitals – a multicenter study) to be conducted by future researchers and a positive outcome of this future Phase III study will positively establish Domperdone as a lactagogue.

Thus, the hypothesis of the study is- Mean volume of milk production of mothers given antenatal domperidone is significantly higher than the mean volume of milk production of mothers given placebo.

MATERIALS AND METHODS

Thirty pregnant women consulting for prenatal check-ups were the target population of the study. All the subjects fulfilled the inclusion criteria of being pregnant women at least 35 weeks age of gestation with adequate prenatal check-ups (4 or more PNCU) at the OPD clinic of the obstetrics and gynecology in the Cagayan Valley Medical Centre (CVMC), Philippines. The exclusion criteria includes: Mothers with absolute contraindications to breastfeeding (mothers with HIV infection, TB, bilaterally infected nipples, on chemotherapy and or radiotherapy and those mothers taking medications for goiter, respiratory distress, who do not plan to breastfeed, gastrointestinal hemorrhage, mechanical obstruction and perforation) and those who are already taking domperidone including the following medications (ranitidine, ketoconazole, metoclopramide, haloperidol, sulperide, chlorpromazine, fenugreek and malunggay).

The written informed consent was obtained from each individual and the ethical committee approved the study. The participants were randomly assigned to one of the two treatment groups: domperidone group (group 1) and placebo group (group 2). Randomization was done using a table of random numbers prepared by a third party not involved in patient care. Randomization assignment was done by draw system from a sequentially arranged sealed opaque envelope. The antenatal domperidone group received 10 mg domperidone capsule orally 3 times daily immediately upon admission. The placebo group also received same colored capsule containing flour three times daily prior to delivery. First dose of the study drug was taken anytime during the active phase of labor. If in case the active phase of labor was prolonged, the 2nd dose was given after delivery. Both groups continued taking the medications up to third day postpartum. Upon delivery non separation of the mother and baby was done for early initiation of breastfeeding. Mothers were advised to breastfeed per demand all throughout the study. Mothers did manual breast milk expression for 15 minutes by hand. Prior to this, they were taught the proper way of breast milk expression by hand (manual attached). Breast milk collection was done on the 18th, 36th and 72nd hours post-partum, respectively. Volume of breast milk expressed was measured in ml and recorded. Expressed breast milk was cupfed to babies. The person giving the study medications was different from the persons monitoring the volume of breast milk.

Mothers' vital signs were noted every shift. Mothers were asked to record any side-effects experienced on a daily chart of the main side effects listed in the Manufacturer's Product. Information to rank the severity of these on a likert scale of none, mild, moderate, severe and extreme like in adverse effects were noted. Treatment was done, in case of headache paracetamol was given and in Extrapyramidal symptoms domperidone was discontinued.

Statistical analysis: The comparison of demographic and clinical profiles of maternal baseline characteristics between domperidone and placebo group was carried out using fisher exact probability test. Difference in milk volume between treatments group were analyzed using Paired T- test. A p-value of 0.05 was considered significant. All the Statistical Analysis was carried out using SPSS 18.0.

RESULTS

Thirty (30) maternal subjects enrolled in this study were randomly assigned to two clinical trial groups: fifteen subjects in the domperidone group and fifteen subjects in the placebo group. Table 1 showed the comparison of demographic and clinical profiles of maternal baseline characteristics between domperidone and placebo group, using fisher exact probability test. The result showed mean volume of milk production for both groups were increasing from the 0 hour postpartum (PP) to the 18th hours PP up to 72nd hours PP. The mean volume of milk and (95% Confidence Interval of the Mean) at 18th hours was 1.61 ml (-2.14 ml to 5.36 ml) was increased to 6.46 ml (-4.3 ml to17 ml) at 36th hours was further increased to 12.39 (-10.99 ml to 35.77 ml) at 72 hours in domperidone group. Whereas, in the placebo group the mean volume of milk and (95% Confidence Interval of the Mean) at 18th hours was 0.26 ml (-0.56 ml to 1.10 ml); at 36th hours was 2.40 ml (-4.45 ml to 9.28 ml) and was 4.89 (-7.55 ml to 17.34 ml) at 72 hours. The mean volume of milk production in the domperidone group was significantly higher at the 18th hours, 36th hours and 72nd hours than the mean volume of milk production at the 18th hours, 36th hours and 72nd hours in the placebo group i.e $P<0.05$ (see Table 2 and Figure).

Table 1: Comparison of maternal baseline characteristics ie maternal demographic profile (maternal age, job employment) and clinical profile (gravida, parity, frequency of PNCUs and manner of delivery) between domperidone group and placebo group, using fisher exact probability test, n = 30.

Baseline Characteristics (Maternal)	(Fisher Exact Test)		Comparability of the Variables
	2-tailed	Statistical Significance	
1. Demographic			
1.1 Maternal Age <30 (DG) vs <30 (PG); 30 & >30 (DG) vs. 30 &>30(PG)	0.7152 (p>.05)	NS	Comparable
1.2 Job Employment Employed (DG) vs. Employed (PG); Unemployed (DG) vs Unemployed (PG)	0.5977 (p>.05)	NS	Comparable
2. Clinical			
2.1 Gravida <2 (DG) vs <2 (PG); 2 & above (DG) vs 2 & above (PG)	1.0000 (p>.05)	NS	Comparable
2.2 Parity 1 (DG) vs 1 (PG) >1 (DG) vs >1 (PG)	1.0000 (p>.05)	NS	Comparable
2.3 Frequency of PNCU's 4-6 (DG) vs 4-6 (PG); 7 & above (DG) vs 7 & above (PG)	0.4497 (p>.05)	NS	Comparable
2.4 Manner of Delivery SVD (DG) vs SVD (PG); CS/OFE (DG) vs CS/OFE (PG)	1.0000 (p>.05)	NS	Comparable

*** NS – Not Significant; SVD-Simple Vaginal Delivery; CS-Caesarean Section; OFE- Outlet Forceps Extraction. DG-Domperdone Group; PG - Placebo Group; PNCU- Pre-natal check-Up.**

Table 2: Mean volume of milk production at 18th hours, 36th hours and 72nd hours postpartum (pp) among the domperidine and placebo group, n=30.

Volume of milk recorded at various hours	Domperidone Group (n=15)	Placebo Group (n=15)
	Mean (95% CI of the mean)	Mean (95% CI of the mean)
Volume of milk (ml) at 18th hours	1.61 ml (-2.14 ml to 5.36* ml)	0.26 ml (-0.56 ml to 1.1 ml)*
Volume of milk (ml) at 36th hours	6.46 ml (-4.3 ml to 17 ml)*	2.4 ml (-4.45 ml to 9.28 ml)*
Volume of milk (ml) at 72nd hours	12.39 ml (-10.99 ml to* 35.77 ml)	4.89 ml (-7.55 ml to 17.34 ml)*

CI: Confidence Interval.

***Denotes: Mean volume of milk (ml) is statistically significant between Domperidome and Placebo group at 18th, 36 and 72 hours, P<0.05 (Paired T-Test)**

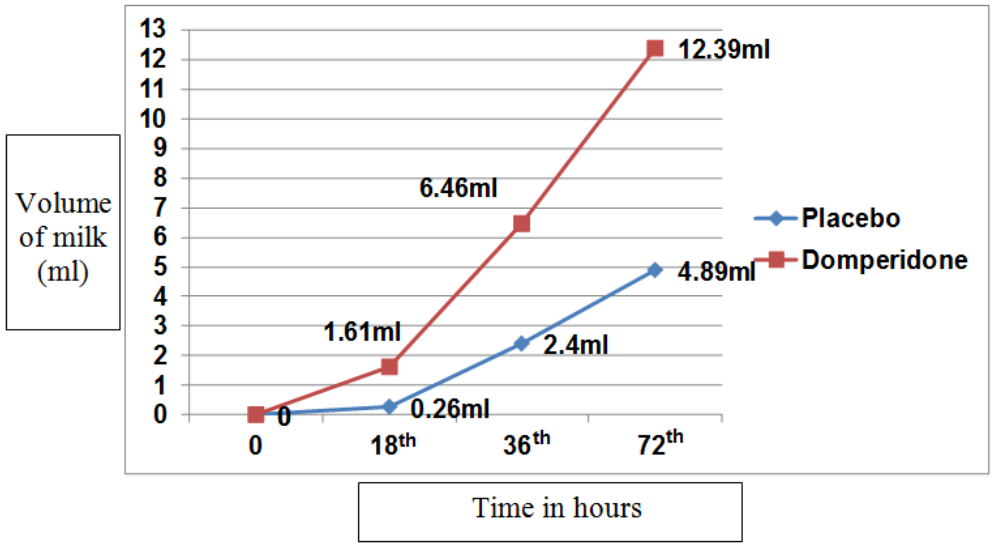

Figure: Line diagram showing the Mean Volume (ml) of Milk Production at 18th hours, 36th hours and 72nd hours Postpartum (PP) between the domperidone and placebo Group, n=30, using Paired T-test P=<0.05.

DISCUSSION

This randomized double blind placebo controlled Phase II clinical trial study aims to determine the effectiveness of antenatal domperidone in increasing breast milk volume among thirty enrolled mothers in labor.

For the maternal baseline characteristics of the two experimental groups such as demographic profile (maternal age, job employment) and clinical profile (gravida, parity, frequency of PNCUs and manner of delivery) all the maternal subjects are comparared as shown in Table 1. The result of this study showed that as for the volume of milk production, the differences in mean volume (in ml) between the domperidone and placebo group was statistically significant at 18 hours PP, 36 hours PP and 72 hours PP. The volume of milk production was higher in the domperidone group than in the placebo group. According to a randomized double-blind placebo-controlled study by Orlando et al. 2009, this drug increases milk production by 44.5% in the domperidome group. By day 5 there was a significantly greater increase in the serum prolactin levels in the domperidone group than in the placebo group which support our result and this is what made the researcher to propose and undertake this study giving domperidone antenatal could possibly address the problem of inadequate breast milk in the first few days post-partum.

Moreover, the volume of milk production was increased in time (from 18 hours to 36 hours to 72 hours PP) in both experimental groups but the increase in the domperidone group was higher than that of the placebo group (Table 2 and Figure). This increase is attributed due to stimulation of pituitary gland thus enhancing prolactin production that stimulates lactation by increasing amount of milk. The underlying mechanism of the domperidone drug is that it undergoes first-pass and gut-wall metabolism, through hydroxylation and oxidative N-dealkylation, it is metabolized to hydroxydomperidone and 2,33-dihydro-2-oxo-1H-benzimidazol-1-propionic acid, respectively.[5-8]

The domperidone drug is an anti-dopaminergic drug which induces lactation by inhibiting endogenous dopamine and thereby increasing plasma prolactin levels. Domperidone is a newly developed anti-emetic is structurally related to the neuroleptic drug droperidol. Domperidone is a dopamine antagonist in vitro; it binds strongly to the dopamine (DA) receptors of the striatal area.[7,8] It is felt that domperidone inhibits dopamine receptors at either the level of the anterior pituitary median eminence or at the tubero infundibular systems, both of which are outside the blood brain barrier. This drug is less lipid soluble, has a higher molecular weight and has lower protein binding.[7] These characteristics may also prevent domperidone from crossing the blood brain barrier, thus causing less extra pyramidal effects that are more commonly reported with the use of other drugs like metoclopramide. It is eliminated 7 hours after single oral and intramuscular administration and the time to peak concentration is 10-30 minutes following intramuscular injection or 30 minutes following oral administration.[5]

However, it is also reported that after starting domperidone (Motilium™), it may take 3 or 4 days before any noticeable effect, though sometimes, mothers notice an effect within 24 hours.[8] It appears to take 2 to 3 weeks to get a maximum effect.[5,8] Hence, in this study it was demonstrated that antenatal giving of domperidone increases the volume of milk production and that volume of milk production is a strong parameter to evaluate the efficacy of domperidone as a lactagogue which reduce the infant mortality rate as per the demopragphics statistics reported by researchers.[9,10] As in a study, on child survival, he found out that among 10 million global deaths of infants and young children, breast feeding can save 1.3 million lives yearly.[11] This study revealed that the risk of death due to infection increased with increasing delay in breast feeding and that partial breast feeding is associated with a 5.7 fold adjusted risk of death due to infection.[11] The study showed that initiation of breastfeeding within the first day or hour of life respectively, can decrease mortality by decreasing ingestion of infectious pathogens, providing many immune-competent factors including immune-globulins and lymphocytes, priming GUT decreasing intestinal permeability. Eventually, close skin to skin contact stimulate mucosa associated lymphoid tissue system.[11]

There is a problem in breastfeeding and the main reason of mothers is inadequate milk supply. The question is if there is any move to alleviate this problem. During the past years, galactagogues were introduced to alleviate the problem such as metoclopramide, domperidone, sulpiride, chlorpromazine, oxytocin and other herbal preparations such as malunggay and fenugreek.[12-14] Metoclopramide has a dose dependent prolactinogenic effect and is recommended in the dose of 10 to 15 mg/day, given orally three times a day, for 1 to two weeks. Natural products such as fenugreek (member of the pea family have been used to increase milk production but no scientific evidence exists that these products are efficacious as galactagogues.[12-14]

CONCLUSION

This study has confirmed the findings of past similar clinical trial studies that antepartum giving of domperidone can enhance the volume of milk production. Further, to assess the safety of the lactagogue effect of Domperidone, it is suggested that multi-center study with a large cohort is needed to carried out in a clinical setting.

Based on previous clinical studies as revealed in the review of literature on the effectivity of domperidone as a lactagogue, the volume of milk production at certain period of time (in hours) PP was adopted as the major/main parameter to be utilized. However, there are other potential surrogate parameters which can be

adopted based on previous studies such as neonatal characteristics like weight loss/weight gain at certain period of time (in days) PP, neonatal number of bowel movements at certain period of time (in hours) PP, urine output at certain period of time (in days) PP and occurrence of jaundice needs to explored further. Thus, it would be great interest for the researcher to adopt the aforementioned surrogate parameters for the future study in addition to the major/main parameter which is the volume of milk production.

REFERENCES

1. Manlapaz Ma. Luisa DV, The first 24 hours: Making an impact on neonatal survival. PSNBM 4th annual meeting and post graduate course on lactation, 2010; 26-27.
2. National Demographic and Health Survey, Philippine National Statistics Office, 2003.
3. Breastfeeding and Maternal Medications. www.scielo.br Accessed October 08, 2011.
4. Orlando P. da Silva, David C. Knoppert, Michelle M. Angelini, Penelope A. Forret. Effect of domperidone on milk Production in mothers of premature newborns: a randomized, double blind, placebo- controlled trial. CMAJ, 2001; 164(1): 17-21.
5. Wan Elise W-X., Davey Kaye, Page-Sharp Madhu, et. al. Dose-effect study of domperidone as a galactagogue in preterm mothers with insufficient milk supply, and it's transfer into milk. British Journal of Clinical Pharmacology, 2008; 66(2): 283-289.
6. Marsha L. Campbell-yeo, MN, Alexander C. Allen, MD, K.S. Joseph, MD, PHD, Joyce M Ledwidge, PDt, Kim Caddell, Bscn, Victoria M. Allen, MD, Msc, and Kent C. Dooley, PHD. Effect of domperidone on the Composition of Preterm Human Breast milk. American Academy of Pediatrics volume 125, Number 2010.
7. Brouwers J, Assies J, Wiersings WM, Huizing G, Tytgat G. Plasma prolactin levels after acute and sub chronic oral administration of domperidone and of metoclopramide: A cross over study in healthy volunteers. Clin Endocrinol, 1980; 12: 435–440.
8. Gabay M. Galactogogues: Medications that induce lactation. J Hum Lact., 2002; 18: 274–279.
9. Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS. Domperidone: A review of its pharmacological activity, pharmokinectics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an antimetic. Drugs, 1982; 24: 360–400.
10. E Anne MacGregor, Migraine in Preganancy and Lactation, A Clinical Review, FFPRHC J Fam Plann Reprod Health Care, 2007: 33(2).
11. Lauer JA1, Betrán AP, Barros AJ, de Onís M. Deaths and years of life lost due to suboptimal breast-feeding among children in the developing world: a global ecological risk assessment. Public Health Nutr., 2006; 9(6): 673-85.
12. Bazzano AN, Hofer R, Thibeau S, Gillispie V, Jacobs M, Theall KP. Ochsner J. A Review of Herbal and Pharmaceutical Galactagogues for Breast-Feeding Review, 2016 Winter; 16(4): 511-524.
13. Forinash AB, Yancey AM, Barnes KN, Myles TD. Ann Pharmacother. The use of galactogogues in the breastfeeding mother- review, 2012; 46(10): 1392-404.
14. Zapantis A, Steinberg JG, Schilit L. Use of herbals as galactagogues. J Pharm Pract., 2012; 25(2): 222-31.