A comparative study on the efficacy of the different galactogogues among mothers with lactational insufficiency

Mary Antonette M. Co, MD* Emilio A. Hernandez,Jr., MD** and Benjamin G. Co, MD***

ABSTRACT

To compare the efficacy of metoclopramide, domperidone, malunggay leaves with milk expression by breast pump vs milk expression using only a breast pump in terms of the volume of milk (mL) and the maternal serum prolactin level. In addition, adverse drug reaction, if any was determined on the mother and the infant with the dose recommended and to correlate the volume of breast milk and the prolactin level. Mothers who delivered to a premature infant <37 weeks gestational age and the baseline milk volume of the mother was <100 mL on the 2nd postpartum day were instructed on how to use a standard breast pump. Milk production was measured and averaged during the first 48 hours baseline period (day 3), 40 mothers were randomized to receive either metoclopramide, domperidone, malunggay capsules or to milk expression by using the standard breast pump alone. Milk volume was tabulated on day 7 and 14. Maternal venous blood for prolactin level was taken on day 3 prior to the start of the intervention, day 7 and day 14. The volume of milk on day 7 and day 14 were significantly higher in the treated group. Domperidone showed the highest mean volume of 335.2 mL on day 7 and 390.56 mL on day 14 followed by metoclopramide, malunggay and the control group. The mothers reported no major side effects and no untoward effects were noted in the infant fed milk expressed while their mothers were taking the galactogogues. Pearson correlation analysis did not show any correlation between the amount of breast milk and the serum prolactin level. Domperidone, metoclopramide and malunggay capsules show promising roles for mothers with lactational insufficiency. Serum prolactin level is not a determinant of success of breast feeding.

Key words: **breast feeding, galactogogues, lactational insufficiency**

There is an alarming decline in both the prevalence and duration of breastfeeding especially in the urban areas. In the Philippines alone, only 55% of mothers initiated breastfeeding soon after delivery but only 22% of these mothers are still exclusively breastfeeding by one month old.[1] One of the most common reasons given was not having enough milk. According to Kauppila A, Anunti and Reece EA, about 20-70% of mothers fail to initiate or maintain adequate lactation. The authors did a pilot study among 10 mothers who delivered to a premature infant <37 weeks at the University of Santo Tomas Hospital and the Ospital ng Maynila Medical Center. It showed that 70% of these mothers had lactational insufficiency i.e. milk volume less than 100 mL on the 2nd postpartum day. Under normal conditions, about 100 mL is available on the 2nd postpartumday.[2]

Galactogogues are agents that enhance milk secretion and improve letdown.[3] Among the galactogogues, metoclopramide, domperidone and malunggay leaves show promising results.

Metoclopramide and domperidone are drugs used primarily for gastrointestinal diagnostics and in treating various forms of vomiting and for organic gastrointestinal disorders. Their effect on lactation by stimulating the release of prolactin have been studied by Brown[4] and Ehrenkranz.[5] Studies by Kauppila[10] and Ehrenkranz[5] showed a significant increase in the volume of milk using metoclopramide while a study by Knoppert DC[6] showed that mothers of premature babies randomized to domperidone had a 44.5% increase in daily milk volume. It is probably by antagonism of the hypothalamic dopaminergic receptor in the pituitary and hypothalamus that indirectly stimulates the secretion of prolactin.[7] There is transfer of metoclopramide and domperidone to the breast milk. However, the amount of the drug received by the infant is much less the maximum daily dose of 500 µg/kg recommended in infants or 100 µg/kg/day dosage that has been given in premature infants.[8,9,10] The study by Ehrenkranz and Ackerman did not report any major side effects by the women and no untoward effects were seen in the infants fed with milk expressed while their mothers were taking metoclopramide.[5]

It is common practice in the Philippines especially in the rural areas to give malunggay leaves (Moringa oleif-

*Neonatology Fellow-in-Training, University of Santo Tomas Hospital
**Chief, Section of Neonatology; University of Santo Tomas Hospital
***Director, Nonavailability Unit; University of Santo Tomas Hospital

èra) as ingredient to the usual viand to postpartal women in order to achieve successful lactation. Dried young malunggay leaves powder being marketed in capsule form was shown to increase the volume of milk and serum prolactin level.[11,12,13]

No available study has been undertaken to compare all 3 active agents. This study compares the efficacy of various galactogogues locally available, i.e., metoclopramide, domperidone, malunggay leaves and milk expression alone among mothers with lactational insufficiency in terms of the volume of milk and the maternal serum prolactin level. Any adverse drug reaction was also noted.

Therapeutic intervention will help mothers with preterm infants <37 weeks who have insufficient milk production to have a successful breastfeeding strategy.

OBJECTIVES

To determine the galactogogue property, if any, of metoclopramide, domperidone, malunggay leaves in terms of the volume of milk and the maternal serum prolactin level; to compare the efficacy of metoclopramide, domperidone, malunggay leaves with milk expression by breast pump versus milk expression using only a breast pump in terms of the volume of milk (mL) and the maternal serum prolactin level; to determine, if any adverse drug reaction on the mother and the infant with the dose recommended; to correlate the volume of breast milk and the serum prolactin level.

MATERIALS AND METHODS

Mothers who delivered to a premature infant <37 weeks gestational age, whose baby was admitted to the Neonatal Intensive Care Unit, and the baseline milk volume of the mother was <100 mL on the 2nd day postpartum were informed about the research project. Inclusion criteria were: healthy mothers with no concurrent medication nor illnesses, mothers with single live infants, mothers of babies with no associated congenital abnormalities and mothers with no breast anomalies. After giving a voluntary informed consent, proper orientation, demonstration and training by the primary author regarding the use of a Gerber battery/electric breast pump was done. Milk production was measured and averaged during the first 48 hours baseline period (day 3), 40 mothers participated in the trial. They were randomized to receive either metoclopramide 10 mg TID, domperidone 10 mg TID, malunggay capsules 250 mg TID or milk expression by using the standard breast pump alone. They were randomized using a controlled block design.

Mothers who participated in the trial were instructed to pump and empty their breast every 4 hours for 10-15 minutes for 14 days. Milk volume was tabulated on days 7 and 14. Patients were followed-up closely during the first 72 hours of the study and 4 more times after discharge. The mothers were instructed how to correctly measure the amount of milk expressed using a standard measuring container.

Maternal venous blood samples were centrifuged and frozen for analysis. Serum core prolactin concentrations were determined using enzyme immuno assay on day 3 prior to starting the intervention. Blood for prolactin level on day 7 and day 14 were taken 1-2 hours after the oral dose and 1-2 hours after milk expression using the standard breast pump. Measurement of side effects was done using a checklist.

Two-way ANOVA was used to determine if there was a significant difference among the 4 groups and one-way ANOVA was used to determine for a significant difference between the groups in terms of volume of milk and serum prolactin level. A p value of <0.05 was considered significant.

Multiple two tailed t-test was used to compare the different groups in terms of the volume of milk and the serum prolactin level. A p value of 0.05 was considered significant.

The Pharmacy, Therapeutics and Research Committee and the Bioethics Research Committee of the University of Santo Tomes Hospital approved the study protocol.

RESULTS

A total of 40 mothers were enrolled, 10 were randomized to each study group. There was 1 patient in the domperidone group who failed to submit her record book and therefore was considered a dropout. The infant of a mother on metoclopramide group died during the $_{10}$th day of the study due to septicemia. Her data was included in the computation. The final data had 11 mothers in the domperidone group, 10 mothers each in the malunggay capsule group, metoclopramide group and the control group.

Single factor ANOVA did not show any significant difference in the maternal age, gravidity, infants' birth weight and gestational ages of the groups. (Table 1)

Two-way ANOVA showed a significant difference among the 3 treatment and control groups. (Table 2)

Using one-way ANOVA, milk volume on day 3 did not show any significant difference. Patients were then started on the different treatment groups. Day 7 and day 14 showed significant difference among the domperidone, metoclopramide, malunggay and the control groups. (Table 3)

An increasing trend in the volume of expressed breast milk toward day 7 and day 14 is noted. Domperidone showed the highest mean volume of 335.2 mL on day 7 and 390.56

n day 14, followed by metoclopra-mide, malunggay and the control roup. Statistical analysis using one-ay ANOVA showed a significant ifference among the groups on day nd day 14.

Multiple two tailed t-test was done to show the difference between comparison groups. Table 4 shows the comparison groups on day 7 and Table 5 shows the comparison groups on day 14.

Statistical analysis showed a significant difference between the treatment groups vs the control group, domperidone vs malunggay and metoclopramide vs malunggay in terms of expressed breast milk volume on day 7 and day 14. However, domperidone vs metoclopramide did not show any significant difference on day 7 and 14. (Table 4 & 5)

Two-way ANOVA showed a significant difference between treatment groups in terms of serum prolactin level but there was no significant difference between day of milk volume collection and between groups vs day of milk volume collection. (Table 6)

Serum prolactin concentration increased significantly among women in the treatment groups on day 7, but showed a slight decline on day 14. One-way ANOVA did not show any significant difference between groups on day 3 and day 14.

Statistical analysis showed a significant difference between treatment groups domperidone vs malunggay, domperidone vs control and malunggay vs metoclopramide while domperidone vs metoclopramide, metoclopramide vs control and malunggay vs control group did not show any statistical significance. (Table 8)

Pearson correlation analysis did not show any correlation between the amount of breast milk and the serum prolactin level. (Table 9)

There were 2 mothers in the metoclopramide treatment group and 1 in the control group who complained of fatigue while 1 patient in the malunggay group complained of tinnitus. Both were not directly related to the drug administration.

Table 1
BASELINE CHARACTERISTICS OF THE DIFFERENT GROUPS

Baseline characteristics	Domperidone x±SD	Malunggay x±SD	Metoclopramide x±SD	Control x±SD	P value
	9	10	10	10	
Maternal age (yrs)	25.67±6.95	27±6.6	24.2±6.2	27.2±7.94	0.43
Gravidity2.1±1.44	2.1±1.79	1.3±0.68	2±0.94	0.45	
NSD:CS	5:4	5:5	8:2	6:4	
History of previous breastfeeding. No. (%)	2/9 (22)	1/10 (10%)	1/10 (10%)	2/10 (20%)	
Infants' birth weight (kilograms)	1.87±0.44	1.717±0.45	1.909±0.48	1.866±0.35	0.77
Gestational age (wks)	34.06±1.97	34.25±2.95	34.6±1.99	34.5±2.02	0.95

Table 2
TWO-WAY ANOVA (MILK VOLUME IN ml)

Source of Error	P value
b/w treatment groups	0.0001
b/w day of ml volume collection	0.0001
b/w group and day of milk volume collection	0.0001

Table 3
BASELINE CHARACTERISTICS OF THE DIFFERENT GROUPS

Postpartum day	Domperidone x±SD (range in mL)	Malunggay x±SD (range in mL)	Metoclopramide x±SD (range in mL)	Control x±SD (range in mL)	P value
Day 3*	15.73±12.04 (2-32.5)	20.3±21.54 (0-71)	43.3±32.77 (0-97)	25.8±28.33 (0-80)	0.101
Day 7	335.2±165.23 (170-690)	180.68±98.22 (13-368.75)	285.2±170.4 (85-610)	92.1±78.33 (5-210)	0.0014
Day 14	390.56±173.52 (160-660)	205.8±110.17 (14-390)	321.7±143.05 (135-675)	73.5±42.88 (6-140)	<0.001

*pre-treatment milk volume

Table 4
COMPARISON OF THE DIFFERENT GROUPS IN TERMS OF THE VOLUME OF MILK (mlL) ON DAY 7

Comparison groups	Volume of milk (mL) day 7 x±SD	P value*
Domperidone vs control	335±165.23 vs 92.1±78.33	<0.001
Malunggay vs control	180.68±98.23 vs 92.1±78.33	0.0389
Metoclopramide vs control	285.2±170.41 vs 92.1±78.33	0.0044
Domperidone vs malunggay	335.2±165.23 vs 180.68±98.23	0.022
Domperidone vs metoclopramide	335.2±165.23 vs 285.2±170.41	0.526 (NS)
Malunggay vs metoclopramide	180.68±98.23 vs 285.2±170.41	0.109 (NS)

*two tailed t-test

Table 5
COMPARISON OF THE DIFFERENT GROUPS IN TERMS OF THE VOLUME OF MILK (ml) ON DAY 14

Comparison groups	Volume of milk (mL) day 7 x±SD	P value*
Domperidone vs control	390.56±173.52 vs 73.5±42.89	<0.001
Malunggay vs control	321.7±143.05 vs 73.5±42.89	<0.001
Metoclopramide vs control	205.8±110.7 vs 73.5±42.89	0.0023
Domperidone vs malunggay	390.56±173.52 vs 205.8±110.17	0.012
Domperidone vs metoclopramide	205.8±110.17 vs 321.7±143.05	0.057
Malunggay vs metoclopramide	390.56±173.52 vs 321.7±143.05	0.357 (NS)

* two tailed t-test

Table 6
TWO-WAY ANOVA (serum Prolactin level in mIU/L)

Source of Error	P value
b/w treatment groups	0.004
b/w day of ml volume collection	0.1387
b/w group and day of milk volume collection	0.7766

Table 7
SERUM PROLACTIN LEVELS (mIU/L) OF DOMPERIDONE, MALUNGGAY, METOCLOPRAMIDE AND THE CONTROL GROUP

Postpartum day	Domperidone x±SD (range in mL)	Malunggay x±SD (range in mL)	Metoclopramide x±SD (range in mL)	Control x±SD (range in mL)	P value
Day 3*	4044.87±2461.5 (442.8-8000)	3149.2±1312.4 (1406-5526)	4064.8±2127.06 (1618-7661)	3244.94±2289.76 (699.7-8000)	0.65
Day 7	5235.44±1672.69 (2452-7791)	2088.68±2175.3 (380.8-7642)	4109.82±2449.0 (657.2-7357)	2812.34±1967.96 (483.2-5086)	0.012
Day 14	3801.8±3036.8 (148.4-7923)	1229.2±1468.64 (241.5-4904)	3547.24±2689.9 (1865.1-8000)	2337.17±2699.9 (118.3-8000)	0.113

*pre-treatment milk volume

Table 8
COMPARISON OF THE DIFFERENT GROUPS IN TERMS OF SERUM PROLACTIN LEVEL (mIU/L) ON DAY 7

Comparison groups	Prolactin concentration (mIU/L) day 14 (x±SD)	P value*
Domperidone vs malunggay	5235±1672.69 vs 2088±2175.31	<0.001
Malunggay vs metoclopramide	2088±2175.3 vs 4109±2449.02	<0.001
Domperidone vs control	5235±1672.69 vs 2812±1967.96	0.0023
Metoclopramide vs control	4109±2449.0 vs 2812.34±1967.96	
Malunggay vs control	2088±2175.3 vs 2812.34±1967.96	0.057
Domperidone vs metoclopramide	5235±1672.69 vs 4109±2449.02	0.357 (NS)

* two tailed t-test

Table 9
CORRELATION VALUES BETWEEN VOLUME OF MILK AND PROLACTIN LEVELS FROM DAY 3 TO DAY 14

Treatment group	Correlation values*	Interpretation
Domperidone group	0.07	Direct poor corrrelation
Malunggay capsule group	-0.21	Inverse fair correlation
Metoclopramide group	-0.38	Inverse fair correlation
Control group	0.22	Direct fair corrleation

* pearson correlation analysis

DISCUSSION

Premature birth accounts for ab 6-15% of the total live births.[19] A qu tion of what to feed these babies bes always raised.. Everyone agrees t breast milk from a mother who del ered prematurely is the most suitab because of its higher protein and el trolyte contents. Mothers with prem ture infants, despite being highly mo vated have difficulty establishing l tation because of absent stimulati from lack of mother-infant contact. add to this difficulty, it takes 3-4 d postpartum for the establishment of adequate milk supply.[18] These proble increase maternal fatigue and anxi resulting to cessation of l tation. Therefore, moth must rely on breast milk e pression until their infants able to suckle directly. M production often falters mothers of premature sick infants when lactatio maintained solely on milk pression. Hence, a numbe medications have been u to enhance milk productio mothers desirous of lacta who are experiencing di culty in establishing maintaining milk producti

The data presented in t study demonstrates a sig cant increasing trend in volume of milk on day 7 day 14 in the domperid metoclopramide and malu gay capsule group (Tabl and 5). This result was demonstrated in the ot studies cited. There is a signific increase in the prolactin level on da for the domperidone and metoclop mide group while malunggay caps did not show a significant increase ble 7). The increase in the volum breast milk did not correspond t increase in prolactin on day 3, 7 and A study by Bohnet and Kato likew

did not sh between p milk prod important tiation of in the mai unanswer ber of pro ling facto rather tha the serur in more th even in th levels.[3] S that serur rous won than prin week hov was sig attributed in recept After the in the r sensitive the reaso old had a with fai breast mi peridone group. R may als lactation play of s

Ano responsi flex" is tocin res sitive to ts anoth lactatio women fortable to have

Lac tritional loric int affects quantity ty affec its seve not app volume.

did not show a significant correlation between prolactin concentration and milk production. Prolactin is the most important hormone identified in the initiation of lactation. However, its role in the maintenance of lactation remains unanswered. It is possible that the number of prolactin receptors is the controlling factor in the amount of breast milk rather than the amount of prolactin in the serum. More receptors may result in more than adequate milk production even in the presence of lower prolactin levels.[3] Studies done in 1988 showed that serum prolactin levels of multiparous women tend to be slightly lower than primaparous mothers in the first week however the volume of their milk was significantly higher. They attributed this to the number of prolactin receptors in their mammary gland.[3] After the age of 35, prolactin receptors in the mammary gland was less sensitive to stimulation.[3] This could be the reason why three women >35 years old had a prolactin level >800 mIU/L with fair increase in the amount of breast milk, 1 patient each in the domperidone, malunggay and in the control group. Results obtained in this study may also signify that successful lactation results from a complex interplay of several hormones.[5]

Another neuroendocrine reflex responsible for the "milk let-down reflex" is secreted with suckling. Oxytocin responsible for this reflex is sensitive to disturbances like stress. This is another factor affecting success in lactation. It is recommended that women should breast feed in a comfortable nonrestricting circumstance to have successful lactation.[16]

Lactating women have higher nutritional requirements. Restricting caloric intake during lactation primarily affects milk quality rather than milk quantity. Volume of milk is principally affected when undernutrition is in severe stage.[15,16] Breast size does not appear to be related to the milk volume.[2]

CONCLUSION

Domperidone, metoclopramide and malunggay capsules show promising roles for mothers with lactational insufficiency. Among the 3 treatment groups domperidone was the most efficacious galactogugue followed by metoclopramide and malunggay. However, the sample size was not large enough to make a definitive conclusion as to which of the 3 agents was definitely more efficacious. Although, all three are comparatively safe drugs with no direct adverse events resulting from their intake, close monitoring of the mother and infant using these drugs for lactational insufficiency is prudent. Serum prolactin level is not a determinant of success in breast feeding.

REFERENCES

1. Helping Mothers to Breast feed. Department of Health, Philippines with the assistance of UNICEF, 1991.
2. CAMERON M. Yngve H. Manual on Feeding Infants and Young Children 3 ed. UNIACC Su~Committee on Nutrition. 1983. pp 81-85.
3. RIORDAN J. Auerbach KG. Breasilfeeding and Human Lactation. Jones and Bartlett Publishers. Boston, MA 1993.
4. BROWN RE. Relactation: An overview. Pediatrics. 1977; 60(1): 116-120.
5. EHRENKRANZ RA, Ackerman BA. Metoclopramide Effect on Faltering Milk Production by Mothers of Premature Infants. Pediatrics. 1986; 78 (4): 614-620.
6. KNOPPERT D MScP. Department of Pharmacy and Pediatrics, St. Joseph's Health Care Centre, London Ontario Canada (personal communication with the author).
7. AMERICAN HOSPITAL FORMULARY SERVICE (AH FS) Drug Information, 2001.
8. BRIGGS GG, Freeman RK, Yaffe SJ. Drugs in Pregnancy and Lactation $_4$th ed. A Reference Guide to Fetal and Neonatal Risk. 1994.
9. LEWIS PJ, Devenish C, Kahn C. Controlled Trial of Metoclopramide In the Initiation of Breasifeeding. Br J Clin Pharmacol. 1980; 9: 217-219.
10. KAUPPILA A, Munti P, Koivisto M et. al. Metoclopramide and Breasifeeding. Transfer into Milk and the Newt)0m. Eur J Olin Pharmacol. 1983; 25: 819-823.
11. ALMIRANTE CY, Lim CHTN. Effectiveness of Natalac as Galactogogue. J of Phil Med Assoc. 1996; 71: 2nd272.
12. ALMIRANTE CY, Lim CHTN. Enhancement of Breasifeeding Among Hypertensive Mothers. Increasingly Safe and Successful Pregnancies. 1996: 279-286.
13. ESTRELLA MCP, Mantaring Ill JBV, David GZ, Taup MA. A doublblind, randomized controlled trial on the use of malunggay (Moringa oleifera) for augmentation of the volume of breastmilk among nonnursing mothers of preterm infants. The Phil J of Pediatrics. Jan-Mar 2000; vol.49 no.1:3-6.
14. JOHNSON LR. Essential Medical Physiology 2nd ed. Lippincott-Raven. 1998.
15. SHERWEN LN, Sooloveno MA, Weingarten T. Nursing Care of the Childbearing Family. 2nd ed. Appleton & Lange. 1995.
16. REECE EA, Ferris AM. Puerperium and Lactation in E. Albert Reece and John C. Hobbins (eds). Medicine of the Fetus and Mother, 2nd ed., Lippincott- Raven Publishers, Philadelphia, 1999 pp.1653-167O.
17. GUYTON A, Hall JE. Textbook of Medical Physiology. $_9$th ed. W.B. Saunders; Philadelphia; 1996.
18. NICHOLS FH, Zwelling E. Matemal-Newt:0m Nursing Theory and Practice 1st ed. W.B. Saunders Company Philadelphia; 1997.
19. ALIKPALA SC, Gatmaltan AC, Isleta PF. High Risk Infants In del Mundo F et al (eds). Textbook of Pediatrics and Child Health $_4$th ed., Quezon Avenue, Quezon City, JMC Press, Inc., 2000 pp.252-255.
20. BOHNET HG, Kato K. Prolactin Secretion during pregnancy and puerperium: Response to metoclopramide and interactions with placental hormones. Obsiet Gynecol 65: 789, 1985.