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Original Article

A Double-Blind, Randomized, Placebo-Controlled Trial, Evaluating the Efficacy of Commiphora Mukul Cream in Improving Breast Engorgement in Breastfeeding Women

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Abstract

Breast engorgement is a common problem during breastfeeding that can lead to early discontinuation of breastfeeding. Commiphora Mukul (C. Mukul) is a medicinal plant with analgesic and anti-inflammatory compounds. The present study was conducted to determine the effect of C. Mukul on improving breast engorgement in breastfeeding women. This study was a double-blind, randomized, and placebo-controlled trial conducted with 100 breastfeeding women, whose symptoms of breast engorgement were randomly allocated to C. Mukul cream group or placebo. Both groups were to rub one fingertip of cream on each breast after nursing 8 times a day for 2 days. The breast engorgement symptoms (severity index = erythema + tension + pain erew assessed by the validated breast engorgement checklist. The severity of breast engorgement before the intervention was not significantly different between the two drug and placebo groups (breast erythema (P=0.78), tension (P=0.85) and pain (P=0.06)), but two days after the intervention, 60% of women in the drug group and 22 % of them in the placebo group scored zero in breast engorgement checklist, though there was a significant difference between the groups (P<0.001). No side effects were observed or reported in either group. According to the findings, Commiphora Mukul cream can improve breast engorgement.

Keywords: Breast engorgement, Breastfeeding, Commiphora Mukul, milk supply, Mothers, Postnatal

1. Introduction

Breast engorgement results in breasts fullness and firmness which is accompanied by pain and tenderness [1]. Primary engorgement is due to interstitial edema and the onset of copious milk production . It typically occurs between 24 and 72 hours postpartum, with a normal range of one to seven days, yet peak symptomatology averages three to five days postpartum; secondary engorgement typically occurs later if the mother's milk supply

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exceeds the amount of milk sucked by her infant [2].

The skin on the breast often appears shiny and nipples look flat and may cause nipple scarring and candida infection .Partial drainage obstructs milk secretion, may cause mastitis [3] and affects the onset and the duration of lactation [4].

Maternal breast engorgement is one of the most common problems [5]. More than two-thirds of women develop breast engorgement by the fifth day, but some women also experience this problem on days 9 and 10 postpartum which consequently affects the start and continuation of breastfeeding [4].

Both pharmacologic and non-pharmacologic therapies have been considered to be beneficial for the treatment of engorgement .There is insufficient supporting evidence for any specific kind of breast engorgement treatment, yet proper size bras, breast binders or sports bras have been recommended for supporting the breasts. Applying warm or cold compresses or a warm shower, and analgesics such as ibuprofen and acetaminophen may decrease the discomfort [1]. The efficacy of treatments such as cold and warm bags, acupressure, oxytocin spray, breast lymphatic drainage, cabbage leaf compress, acupuncture, and Gua-Sha massage have been studied which resulted in conflicting results and insufficient evidence to support these treatments [6]. Three trials looking at cabbage leaves showed no treatment difference between room temperature and chilled cabbage leaves, between chilled cabbage leaves and gel packs and between cabbage cream and the inactive cream; however, all forms of treatment provided some reliefs [7]. The results of a randomized clinical trial conducted to assess the effect of alfalfa leaf compress plus hot and cold compresses on breast engorgement showed that alfalfa leaf compress significantly reduced these verity of engorgement compared to mere hot and cold compresses [8]. There are many herbs in traditional medicine for treating breast engorgement, such as peppermint and garden sage, which reduce breast engorgement in both oral form and oil massage resulting in subsequent reduction in milk production [9].

The World Health Organization recommends using traditional medicine in healthcare programs. Generally, herbal compounds contribute towards reducing pain and inflammation by inhibiting inflammatory pathways and reducing secretion of prostaglandins and nitric oxide [10, 11].

The resin secreted by the plant Commiphora mMukul known as guggul (bdellium) is one of the widely used drugs in Ayurveda for the treatment of several disorders such as gout, arthritis, rheumatism, obesity, hyper-cholesterol and inflammation.

Guggul contains diterpenoids, triterpenoids (guggulesterone), steroids, long chain aliphatic tetrols, aliphatic esters, ferulates, lignans carbohydrates, and a variety of inorganic ions besides minor amounts of sesamin and other unidentified constituents [12, 13]. Jiang *et al*. indicated that guggulesterone targets the B-Catenin transmission pathway in breast cancerous cells that induce inhibition of growth and apoptosis of human cancer cells [14]. Guggulesterone exhibits inhibitory effects on protein-kinase microtubule, and cause a reduction in certain inflammatory mediators such as alpha-tumor necrosis factor and interleukin-2 in peripheral blood mononuclear cells, which shows that C. mukul has anti-inflammatory property through inhibition of protein-kinase microtubule regulating various inflammation-related genes [15]. The results showed that tri- and diterpenoids were responsible for the anti-inflammatory property .Pure biological effects due to exposure to guggulesterone include attenuated production of IL-2, IL-4 and interferon-G, and also proliferation of the T cells. Their sesquiterpenoids possess antimicrobial, analgesic, and smooth muscle relaxant effects. Cytotoxic and steroidal lignans were suitable for anticoagulative, anti-inflammatory, hypolipidemic, and analgesic function [13, 16]. The methanolic extract inhibited nitric oxide production in lipopolysaccharide activated mouse peritoneal macrophages. A steroid (from the plant) tested in rats for inhibition of inflammation was induced by Freund's adjuvant. It inhibited the full development of the primary and secondary lesions in adjuvant arthritis. Guggul had more efficacy than ibuprofen and both had synergistic effect. The study proved that guggul could serve as a carrier for entrapping drugs and for their sustained release action. Several animal studies have demonstrated the effectiveness of guggul extract in standard osteoarthritis models.

C. Mukul generally was admitted as relatively safe (GRAS). There is little or no information on toxicity with the use of guggul [12]. No studies of the side effects of topical administration of guggul cream in lactating women were identified.

In Traditional Medicine of Kerman City (Iran), some local people has used from C. Mukul gum for improving breast engorgement in breastfeeding. Given the importance of nursing and the high prevalence of breast engorgement and its effects on early discontinuation of nursing, the present study was conducted to determine the effectiveness of C. Mukul cream on improving breast engorgement during lactation.

2. Materials and Methods

2.1. Study Design and Random Allocation

The present randomized, double-blind, and placebo-controlled clinical trial was conducted in health centers (Afzalipur and Arjomand Hospitals) in Kerman during January to June, 2017, using a parallel design and based on the ethical criteria of Helsinki protocol (code : IRCT2017062633812N2). The study objectives and outcomes were explained to women who had given birth, and informed consents were obtained from those willing to

take part. Initially, 110 nursing women were selected. Then, based on inclusion and exclusion criteria, 100 women were selected and received explanations about the study objectives. Balanced block-randomization method with block size of four was used in Research Analysis and Statistics (RAS) software for generating random blocks was utilized.

2.2. Sample Size

Given that the present study had two arms, equation 1 was used to calculate sample size. Based on previous similar studies, π_1=9.02 and π_2=0.27, the effect size was found to be 0.27 . Taking the first order error of 0.05 and power of 80% into account, the sample size was calculated as 48 women per group .To compensate the possible sample loss, an extra 15% was added, making the final total sample size 110 women.

$$n= [\frac{Z\alpha_{/2}\sqrt{2\pi_1(1-\pi_1)}+Z_\beta\sqrt{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}}{\pi_1-\pi_2}]^2$$

(Equation 1: The study sample size)

2.3. Inclusion and Exclusion Criteria

Inclusion criteria were Iranian nationality, 1 to 15 days after childbirth, with minimum score of 2 and maximum of 19 in breast engorgement checklist, and sublingual temperature of less than 38°C, with breast engorgement symptoms in the first 15 days following childbirth, no breast abscess or mastitis, no contraindication to nursing, no allergy to any herbal medication, nursing every 2 to 3 hours, no history of breast surgery, with singleton and term infant weighing between 2500g and 4000g and able to suckle. Exclusion criteria were allergy to Commiphora mukul, body temperature >38°C, use of oral and topical chemical or herbal analgesics or hot and cold water compress and acupressure during the study, use of a pacifier, breast pump, formula, or nipple shield during the study, infant hospitalization for any reason, contraindication to nursing by mother during the study, and mother's unwillingness to take part.

2.4. Intervention

C. mukul gum (Persian name: Moql-e Azraq) (from Burseraceae) was procured from the herbal market in Kerman City in October 2016, then extracted with methanol (maceration X 3), and after condensation and evaporation of the solvent, mixed with a base cream (5%) and turned into 60g tubes. The creams were prepared in Pharmacognosy Lab, Shahid Beheshti Univ. Med. Sci. After explaining the study objectives and obtaining written consents, both *C.* mukul and placebo groups were trained for correct nursing and hygiene before the intervention, mothers' temperature was measured and recorded using a mercury thermometer .Then, after demographic details form was completed for each mother, these verities of breast engorgement based on breast engorgement checklist were measured by the researcher and recorded in the relevant checklist. Both groups were to rub one fingertip of cream on each breast after nursing eight times a day for two days, in a way that each breast was completely covered by cream .Then, mothers were asked

to visit for assessment two days later, and levels of pain, erythema and skin stretch were measured and recorded by the researcher, and the breast engorgement checklist was completed. Researcher's phone number was made available to mothers to contact her in case of any problems or complications, unwillingness to continue, and recurrence of breast engorgement.

2.5. Data Collection Tools

In the present study, data collection tools included demographics and obstetrics questionnaire, containing questions about personal details (mother's age, education, and occupation) and obstetrics details (type of labor, nursing status, and the start of current nursing). Breast engorgement observation checklist included erythema (no redness= 0, redness in patches in a limited area= 1, full redness in a limited area= 2, shiny redness in a limited area= 3, and shiny redness over most of the breast tissue= 4), breast tension (no changes = 0, firm and no tenderness= 1, tense but not uncomfortable= 2, tense and uncomfortable= 3, tense and painful= 4, and very tense and very painful= 5) and breast pain score (no pain= 0, to severe pain= 10). The validity of demographic questionnaire was assessed using content validity. Reliability of breast engorgement checklist has been confirmed in various studies for days 3,4 and 5 by Kvist *et al.* with Cronbach's alpha from 0.79 to 0.82 and 0.81 [17]. Reliability found in Moradzadeh study using an equivalent forms reliability was 0.8 [18]. Total breast engorgement score is 19. In the present study, breast engorgement recovery meant a score of 0 in the breast engorgement checklist.

2.6. Statistical Analysis

Data were analyzed in SPSS-16. Normal distribution of data was assessed using Kolmogorov-Smirnov test . To compare baseline data, t score and Chi-square tests were used. To compare the mean scores of the two groups after intervention, the covariance analysis was used, and the two variables of the number of pregnancies and the pre-intervention score were included as covariates. Quantitative data were presented in the form of mean ±SD, and qualitative data were shown as numbers. The significance level was (% 0.05).

3. Results and Discussion

A Total of 10 women were excluded from the study including 6 women from the medication group and 4 from the placebo group, as a result of using anti-inflammatory medications, hospitalization of the newborn, and being prohibited from nursing and dissatisfaction. A total of 100 women in two groups of 50 people completed the interventions (Figure 1).

Mean age was 30.36± 5.58 years in the medication group and 28.48± 5.86 years in the placebo group .Both groups matched in terms of education (P=0.817), occupation (P=0.249), and mode of childbirth (P=0.221). Mean onset of breast engorgement was 3± 2.31 days in the medication group and 3.78± 2.06 days in the placebo group, with no significant difference between them before the intervention (P=0.78) (Table 1).

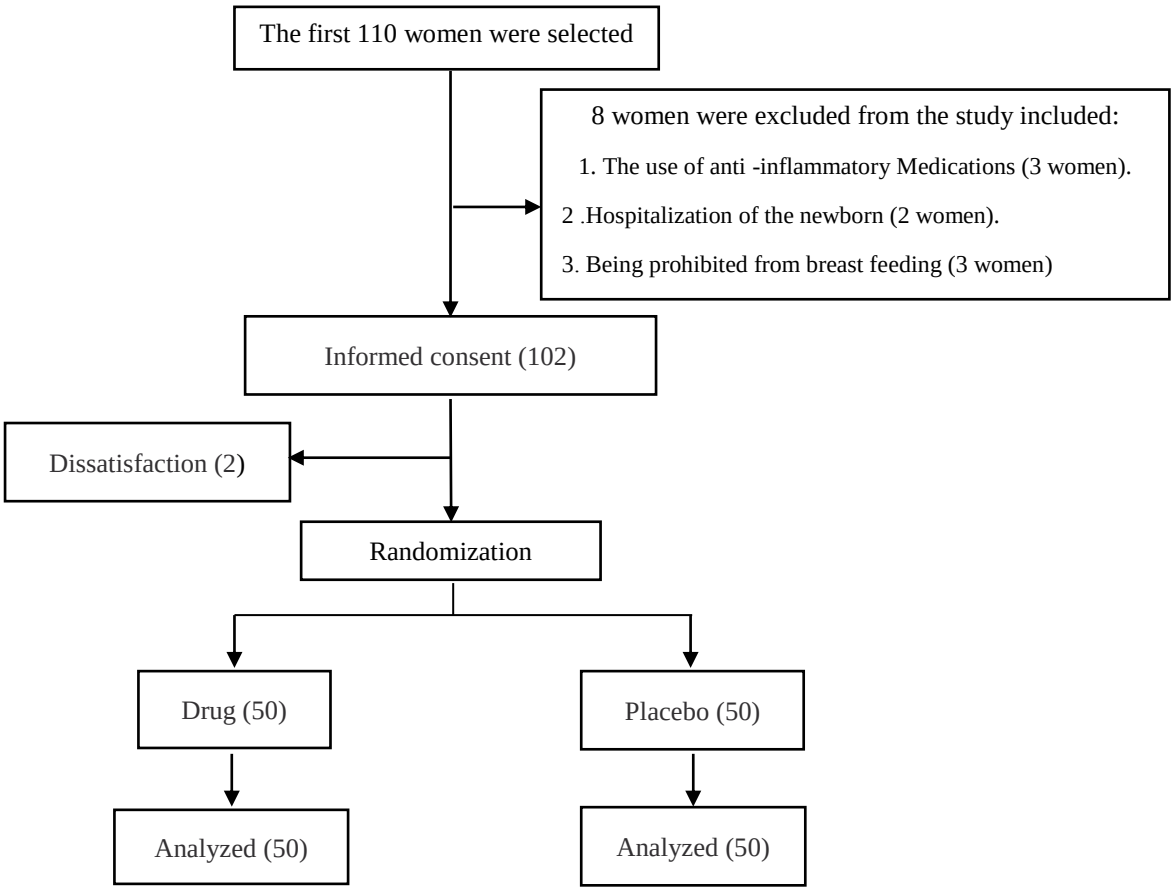


Figure 1. Flowchart of study.

Table 1 .Baseline data in the intervention and control groups.

Variable/Group		Drug	Placebo	Sig.
Education	High school and lesser	13(26%)	12(24%)	0.817
	Diploma and Higher	37(%٧٤)	38(76%)	
Job	House wife	41(82%)	45(90%)	0.249
	Employed	9(18%)	5(10%)	
Type of labor	Normal delivery	17(34%)	23(46%)	0.221
	Cesarean	33(66%)	27(54%)	

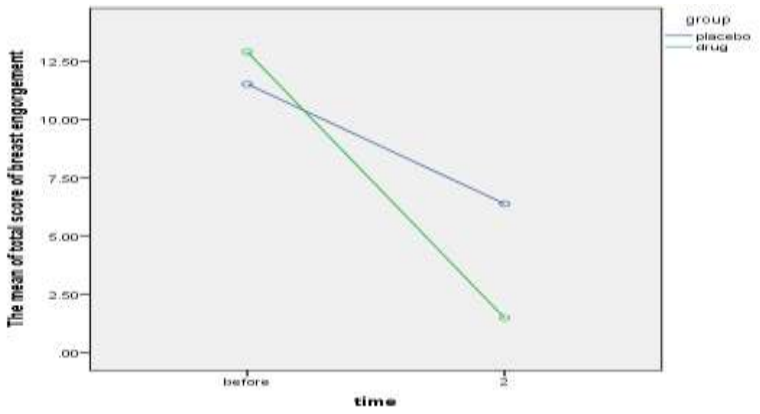
Table 2 shows a comparison of the two groups in terms of breast erythema, tension, and severity of pain. No significant difference was found between the two groups in breast Erythema (P=0.78), tension (P=0.85) and pain (P=0.06) before the intervention, but after the intervention the numbers were significantly lower in the drug group compared to the placebo group (P<0.001). Severity of breast engorgement before the intervention was not significantly different between the two groups (P=0.09), but two days after the intervention there was a significant difference between the two groups (P<0.001). No medication side-effects were observed or reported in either group.

The covariance analysis was also used to compare the mean total score of breast engorgement after intervention in the placebo and drug group. The two variables of the number of pregnancies and the pre-intervention score were included as covariates. According to the results, the mean score in the placebo group was 5.69 which is more than the intervention group (Graph 1).

The present study showed that *C.* Mukul cream improves breast engorgement. The severity of symptoms of breast engorgement, including erythema, breast tension, and pain showed a significantly greater reduction in the intervention group compared to the placebo group.

Table 2 .Comparison of the two groups in terms of scores of Erythema, Tension, and pain after the intervention.

	Variable	**Before beginning intervention**		**p-value**	**After beginning intervention**		**p-value**
		Drug	Placebo		Drug	Placebo	
Erythema	No redness	2 (4%)	0(0%)	P=0.78	43(86%)	22(44%)	P<0.001
	Redness in patches in a limited area	6(12%)	12(24%)		6 (12%)	12(24%)	
	Full redness in a limited area	12(24%)	15(30%)		1(2%)	8(16%)	
	Shiny redness in a limited area	18(36%)	14(28%)		0(0%)	7 (14%)	
	Shiny redness over must of the breast tissue	18(36%)	9(18%)		0(0%)	1(2%)	
Breast tension	No changes	0(0%)	0(0%)	P=0.85	30(60%)	12(24%)	P<0.001
	Firm and no tenderness	1(2%)	0(0%)		6(12%)	4(8%)	
	Tense but not uncomfortable	3(6%)	1(2%)		11(22%)	7(14%)	
	Tense and uncomfortable	12(24%)	25(50%)		2(4%)	14(28%)	
	Tense and painful	20(40%)	17(34%)		1(2%)	11(22%)	
	Very tense and very painful	14(28%)	7(14%)		0(0%)	2(4%)	
The mean of breast pain		6.32±2.86	5.52±2.26	P=0.06	0.56±1.28	3.04±2.54	P<0.001



Graph 1. Comparison of the total score of breast Engorgement after intervention in the placebo group and drug group.

The results of several studies confirm the anti-inflammatory and anti-arthritic effects of guggul. Their anti-inflammatory and anti-arthritic effects were also observed in animal. Guggul had more efficacy than ibuprofen and both had synergistic effect. Several animal studies have demonstrated the effectiveness of guggul extract in standard osteoarthritis (OA) models and also had antimicrobial (sesquiterpenoids, steroidal lignans), analgesic (essential oil, chloroform extract, sesquiterpenoids), and antiproliferative (methanol extract, Steroids) effects . It was also used in a study as an ointment for ulcers [12]. Another possible mechanism of C. Mukul effect on passive avoidance learning can be involved in the AChE inhibitory potential of plant. Besides flavonoids, C. Mukul is rich in guggulsterone. On the other hand, antioxidant and anti-inflammatory effects are relevant to each other [19]. Considering the effects of *C.* Mukul resin compositions, it seems that an ointment made from C. Mukul resin may prevent complications of breast Engorgement, like breast mastitis and fissure, in addition to breast cancer in women.

Herbal compresses have been used for hundreds of years and are accepted for the analgesic and anti-inflammatory indications. These indications include labor pain reduction and milk induction [20].

The results of randomized clinical trial by Khosravan *et al.* showed that alfalfa leaf compress combined with hot and cold compresses had a more significant effect on reducing this verity of breast engorgement compared to hot and cold compress alone. The similarity factor of the previous study, in addition to the checklist, is the use of the medicinal plant in the intervention group. This study measured the severity of breast engorgement in a daily manner up to six days after intervention. It was 9.15± 2.41 before the intervention and 3.35± 2.47 two days after. In our study, the mean severity of the breast engorgement was 4.56± 12.90 before intervention and 1.48± 2.50 two days after. The limitations of their studies were the small number of samples and no placebo [8]. The hollyhock leaf helps soothe the irritated tissues and the inflamed forms. The result of this study is in line with the results of the present study.

A systematic study (2016) conducted by Joanna Briggs Institute to determine the effect of cabbage leaf on breast engorgement showed that the leaf reduces pain score, but no significant supporting evidence was provided to show the reduction in engorgement [6, 21]. But a study finding (2017) revealed that there was a significant reduction in breast engorgement with chilled cabbage leaves application among postnatal mothers .This study measured the severity of breast engorgement 1, 2, and 3 days after intervention. Two days after the intervention, the severity of breast engorgement reached 1.90± 0.76 from 3.63± 0.43 [22]. The result of this study is in line with the results of the present study.

In the study of Alam al-Hoda *et al.* (2014) examined the effect of *Aloe vera* gel on the improvement of nipple pain in 110 lactating

women, a significant decrease was observed in pain score in the group taking *Aloe vera* gel on the tenth and fourteenth days after the intervention ($p < 0.001$) [23]. In the study of Shah-rahmani *et al*. (2016) that investigated the effect of jujube fruit lotion on the improvement of nipple pain, a significant decrease was observed in pain severity score on the seventh and fourteenth days after the intervention ($P < 0/001$) [24]. The flavonoid in jujube and *Aloe vera* is similar to bdellium. Flavonoids have anti-inflammatory and anti-allergic properties due to decreased expression of nitric oxide and decreased secretion of histamines. Flavonoids also inhibit pain by influencing gamma-aminobutyric acid (GABA) receptors. The results of these studies are consistent with the present study.

In the study of Ketsuwan *et al*. (2018), the severity of breast engorgement was reduced in the two groups of plant compress (consisting of dried herbs such as *Z. cassumunar* rhizomes, *C. longa* rhizomes, *Cymbopogon citratus* leaves and leaf sheaths, *Acacia concinna* leaves, *Tamarindus indica* leaves, *Citrus hystrix* peels, *Blumea balsamifera* leaves, salt, and camphor) and warm compress. However, the decrease in the severity of engorgement was greater in the plant compressor group. There was also a statistically significant difference between the two groups under study ($P < 0.001$) [25].

In a study by Monazami *et al.* (2019) studying the effect of warm ginger compress on the severity of breast engorgement showed that the mean severity of total breast engorgement in the right and left breast decreased in the warm ginger compress group and the control group after the intervention, but the severity of breast engorgement was significantly more effective in the warm ginger compress than in the control group ($P < 0.001$) [26]. Ginger extract in these studies reduced the levels of prostaglandins and leukotrienes (inflammatory mediators) and thereby reduced pain. This mechanism is consistent with the mechanism of bdellium to reduce pain.

Previous research showed that progesterone-containing gel could be administered in heavy breast engorgement after lactation is initiated. Application of the gel on the breast skin improvesd swelling, and reduced engorgement and tenderness in 15–20 minutes [27]. According to one observation, within 20 min application of 2.5–3 g of the Progestogel on the breast skin did not result in reducing breast swelling, engorgement and tenderness. After 20 minutes, transdermal application of Progestogel did not reduce the degree of engorgement of the mammary glands in the postpartum period [28].

In this study, C. Mukul mechanism of action in relieving breast engorgement is probably by relieving the inflammatory response outside the lactiferous ducts and increasing the flow of milk out. We did not find any studies on the effect of C. Mukul on breast engorgement. However, the results of the present study can provide a source of support for herbal medicine in treating breast engorgement.

Table 3. Comparison of the mean total score of breast Engorgement after intervention in the placebo group and drug group.

					95 % Confidence Interval	
Variable	**B**	**Std .Error**	**t**	**p-value**	**Lower Bound**	**Upper Bound**
Intercept	-5.208	1.485	-3.506	.001	-8.157	-2.260
engorgement.pre	.431	.085	5.075	.000	.263	.600
N pregnancy	.426	.297	1.433	.155	.-164	1.015
[group=placebo]	5.691	.722	7.882	.000	4.258	7.124
[group=drug]	Reference group	.	.	.	.	.

4. Conclusion

Commiphora mukul cream was able to improve breast engorgement, and therefore it can be used for treatment of breast engorgement.

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