ORIGINAL ARTICLE

The Efficacy of Steamed Ginger Extract versus Placebo for Pain Relief at the Perineum and Uterus in First Normal Postpartum Women

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Background: Perineal and uterine pain are common postpartum complaint.

Objective: To compare the efficacy of steamed ginger extract, paracetamol, a stand analgesic used in Western medicine, and placebo for pain relief at the perineum and uterus in first normal postpartum women.

Materials and Methods: First pregnancy, postpartum women, who had a normal vaginal delivery, were given 3-day 200 mg tid of ginger extract/placebo capsules, or up to 500 mg qid paracetamol in an open randomized (1:1:1) trial. All drugs were given within two hours of delivery. The Numerical Rating Scale was used for pain assessment at 2, 24, 48, 72 hours postpartum. Ninety-nine women were recruited with similar demographic characteristics at the postnatal ward of Thammasat University Hospital.

Results: All groups showed decreasing mean perineal and uterine pain scores over time. The only significant differences in mean scores were seen for perineal pain at 24, 48, and 72 hours in the ginger extract versus the placebo arms at 3.97 versus 6.3, 2.48 versus 6.09, and 1.42 versus 2.61, respectively. There were no adverse drug reactions reported in any of the three arms.

Conclusion: Ginger extract capsules showed promising results and having no adverse reactions, so this should be developed further.

Keywords; Steamed Ginger Extract; Perineum Pain; Postpartum Women

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The most common symptoms that occur in the postpartum period are perineum pain, breast engorgement, and discomfort after vaginal delivery. Perineal pain decreases within three days after delivery. In Thai traditional scripture for women's health, the Mahachotharat scripture, there are 85 remedies for blood circulation and pain management, in particular, 44 remedies contain ginger (*Zingiber officinale* Roscoe, Zingiberacae)[1]. As a food and beverage, ginger is widely used for several clinical indications, including postpartum pain, nausea and vomiting due to motion sickness, and to promote early ambulation and breast feeding[1]. The ginger rhizome contains both the flavor and pungency of a spice, oleoresin, and essential oils, gingerol, and shogaols[2]; both are active ingredients, and both are used in traditional medicines[3]. Gingerols, the major components in fresh ginger rhizomes, are a series of homologues with varied unbranched alkyl chain lengths, whereas shogaols are a series of homologues derived from gingerols with dehydration at the C-5 and C-4 positions during long-term storage or thermal processing[4]. Previous research had shown that the 95% ethanol extract of steamed ginger, which had a high phenolic content, has an inhibition effect on prostaglandin E2 (PGE_2) and nitric oxide (NO) release with IC_{50} value of 0.40±0.06 µg/mL and 13.47±0.20 µg/mL, respectively[5]. Both inflammatory mediators

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are implicated in the pathogenesis of pain. By high-performance liquid chromatography (HPLC) analysis, 6-gingerol and 6-shogaol were the main compounds detected in the 95% ethanol extract of steamed ginger[6], and it has been shown that 6-gingerol and 6-shogaol have antioxidant, anti-inflammatory, and antibacterial properties[7-9]. For these reasons, the authors undertook to assess the postpartum analgesic efficacy of steamed ginger extract and reported the results herein.

Materials and Methods

Study design

The present study was a randomized controlled triple-arm parallel clinical trial with one experimental, a placebo, and a positive control arm to assess the analgesic efficacy against postpartum pain in women following their first normal vaginal labor. The study took place at Thammasat University Hospital between July 2017 and July 2018 and was approved by the Ethics Committee of Faculty of Medicine, Thammasat University, Thailand (number of COA 100/2558). All subjects were informed of the study details and were free to leave the study at any time.

Inclusion and exclusion criteria

The inclusion criteria were healthy women aged 20 to 34 years, first normal labor, no history of pregnancy toxaemia, nor liver or kidney disease or gastrointestinal bleeding during pregnancy, not participating in another research project, no postpartum hemorrhages, willing to sign consent form, on regular medication, and did not smoke or drink alcohol during their pregnancy.

The exclusion criteria were allergic to modern medicine or herbal remedies and not following the treatment correctly. The discontinuation criteria during the trial were developing allergic reaction or a serious adverse event to the study drugs, and not following the study protocol.

Sample size

Sample sizes were based on the necessity to demonstrate a significant difference among steamed ginger extract, placebo, and standard synthetic drug. The sample size was calculated to be at least 30 women per group. This calculation was based on a population eta-squared of 0.10 and 0.80 power[10]. With adjustment for 10% dropout rate, the sample size was 33 cases in each group. The sample selection consisted of simple random sampling by population criteria and dividing sample into the following three groups with group 1, the experimental group, receiving 100 mg ginger extract in capsules, two capsules of 200 mg, three times a day for three days, group 2, the control group, receiving 500 mg placebo capsules, to take two after meal, three times a day for three days, and group 3, the positive control group, receiving 500 mg standard synthetic drug (SSD) to use as required.

Raw materials and drug preparation

Raw materials: Fresh ginger rhizomes used in the present study were from plants grown under Good Agricultural Practice (GAP) at Nam Nao District, Phetchabun Province, Thailand. The ginger rhizomes were cleaned, washed, air dried, autoclaved at 121°C and 15 psi for 15 minutes, and grounded to powder. The powder was macerated in 95% ethanol for three days and filtered through Whatman No.1 filter paper, the filtrate dried by rotary evaporator. The percentage yield of the 95% ethanol extract of steamed ginger, ginger capsule, was 4.71%.

Preparation of steamed ginger extract and placebo capsules:

- Preparation of steamed ginger extract capsules: The capsules were prepared in the Center of Excellence in Applied Thai Traditional Medicine Research (CEATMR), Thammasat University, Thailand. Each capsule contained 100 mg ginger extract blended with Avicel® PH 102 (microcrystalline cellulose PH 102) as excipient. The blending was achieved by gliding Avicel® PH 102 using AEROSIL® colloidal silicon dioxide through strainer number 80 and then mixing the two together using a mortar. The mixture was then glided through strainers 80 then 100 until the powder was uniform. Lubricant was then mixed into the final product and then put into capsules.
- Preparation of placebo capsules: Placebo capsules were filled with lactose monohydrate and were labelled "0". The capsules were 500 mg/capsule.
- Positive control: This was paracetamol group, administered at a dose of 1 gm every six hour.

Capsule dose calculation

The dose of the ginger capsules used in the present trial followed the Reference Dose (RfD) process, which was the appropriate dose a person can ingest every day, according to the U.S. Environmental Protection Agency (EPA) and the U.S. Food and Drug Administration (FDA) guidelines.

The RfD was calculated using the formula:

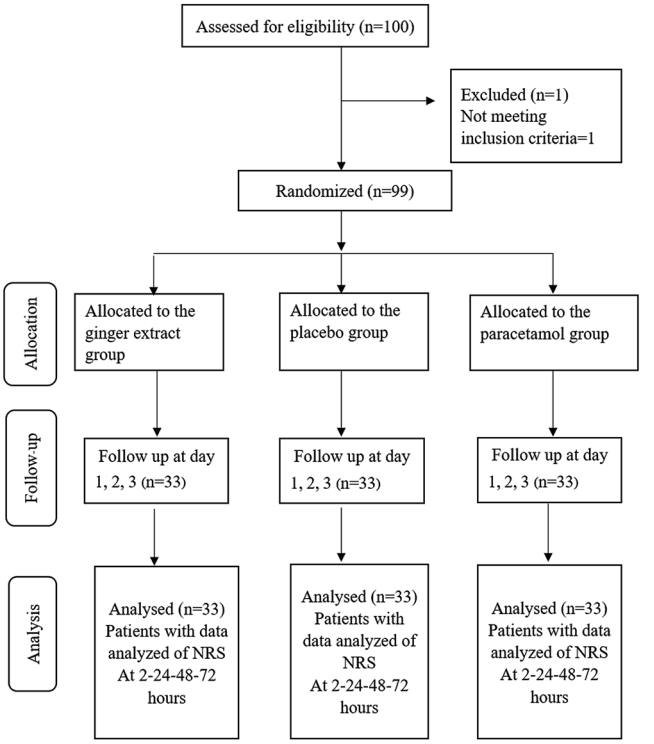

Figure 1. CONSORT flow diagram of participants through the study.

$$\frac{\text{NOAEL} \times \text{mean weight pregnant woman}}{UF_s \times UF_H}$$

NOAEL was the no-observed-adverse-effect-level, primarily established from the preclinical studies. Uncertainty factors (UF) were applied as powers of 10 (i.e., tenfold reductions of the NOAEL) to allow for interspecific variability (UF_s) and intraspecific variability (UF_H) i.e., animals and humans, respectively[11]. For a mean weight of 63.8 kg in pregnant Thai women, the dose was 638 mg/day.

Randomization

Data collection followed randomization were done using even weeks for allocating the ginger capsules and odd weeks for the placebo and paracetamol. Sequentially numbered sealed envelopes containing the treatment were used to allocte treatment. These envelopes were kept with the midwife who opened each envelope when a new participant was recruited at the time of her delivery. All women received the enclosed capsules three times a day for three days postpartum, with the first dose starting within two hours after her delivery.

Data collection

Standardized case report forms were used to collect relevant data such as demographic, delivery, pain scores record. The demogroahic data included age, level of education, occupation, income per month, weight, height, and body mass index. Details of the preganancy and delvivery recorded gestational age, progression of labor, type of perineum trauma, the use of episiotomy, and a maternal assessment two hours after delivery for temperature, pulse, systolic and diastolic blood pressure, blood loss, level of feeling, uterine contraction, bleeding per vagina, gender and weight of the newborns, and Apgar score. Pain was assessed using the numerical rating scale (NRS) by Marrazzu et al. (2015)[12], a method for recording pain scores in specific anatomical and scaled from 0 for no pain to 10 for the worst pain ever. Pain scores were recorded at 2, 24, 48, 72 hours after delivery. Adverse drug reactions were recorded if an adverse event was considered drug related. The following adverse events were itching, rash, muscle pain, muscle weakness, wrist pain, ankle pain, facial swelling, lymphadenitis, eye lid swelling, angioneurotic oedema, glossitis, Hand-Foot syndrome, swollen feet, dyspnea, chest pain, palpitations, tachycardia, dizziness, nausea, vomiting, flatulence, constipation, diarrhea, insomnia, anorexia, bladder irritability, dysuria, and fatigue.

Table 1. The Demographic characteristics

Demographic information	Population group			p-value
	Ginger extract (n=33)	Placebo (n=33)	SSD (n=33)	
Age (years); median (min, max)	24 (22, 28)	24 (22, 28)	27 (22, 28)	0.559[a]
Education level; n (%)				0.566[b]
Unlettered	-	1 (3.0)	-	
Primary education	15 (45.5)	1 (3.0)	2 (6.1)	
Secondary education	9 (27.2)	18 (54.5)	14 (42.4)	
Diploma	7 (21.2)	6 (18.2)	8 (24.2)	
Bachelor's degree	1 (3.0)	7 (21.2)	8 (24.2)	
Master's degree	1 (3.0)	-	1 (3.0)	
Occupation; n (%)				0.240[b]
Housewife	7 (21.2)	5 (15.2)	7 (21.2)	
Merchants	5 (15.2)	2 (6.1)	4 (12.1)	
Labourer	20 (60.6)	21 (63.6)	15 (45.5)	
Civil servant/SOE	1 (3.0)	1 (3.0)	3 (9.1)	
Other	-	4 (12.1)	4 (12.1)	
Income per month (Baht); median (min, max)	12,000 (8,000, 15,000)	14,000 (8,600, 16000)	14,520 (10,000, 17,500)	0.544[a]
Weight (kg); mean±SD	65.52 (13.37)	64.56 (10.07)	66.11 (10.12)	0.854[c]
Height (cm.); mean±SD	158.64 (6.06)	159.12 (6.39)	159.79 (5.93)	0.746[c]
Body mass index (kg/m^2); mean±SD	25.95 (4.60)	25.36 (3.55)	25.77 (3.26)	0.817[c]

SSD=standard synthetic drug; SOE=state owned enterprise; SD=standard deviation

[a] Kruskal-Wallis H test; [b] Fisher's exact test; [c] One-way ANOVA

Statistical analysis

In the clinical research form, all information was recorded. The categorical data between groups were analyzed by Fisher's exact test, as appropriate, and continuous data between arms were analyzed by the Kruskal-Wallis H test. All analyses were two-sided and a p-value of less than 0.05 was considered statistically significant using a Stata, version 14 (StataCorp LP, College Station, TX, USA).

Results

Demographic and obstetric information

One hundred women were assessed for eligibility. One woman did not meet the inclusion criteria. Ninety-nine first normal postpartum women were recruited into the study, 33 per arm. There were no significant differences among the three groups in terms of their demographics such as age, education level, occupation, income per month, weight, height, and body mass index as shown in Table 1. Maternal clinical data two hours after delivery and newborn data are shown in Table 2. There were no significant differences regarding their vital sign, blood loss, level of feeling, uterine contraction, vaginal bleeding, perineum wound, and paracetamol receiving. The mean gestational ages were 39 weeks (ginger capsules), 38 weeks (placebo), and 39 weeks (paracetamol), respectively. The most frequent type of perineal trauma was a second degree cut from a right mediolateral episiotomy. All newborns had Apgar scores of 10 at five minutes and no significant differences among the three groups in terms of newborn gender and weight as shown in Table 2.

Pain scores post delivery

Postpartum pain score at perineum and uterus were derived from numeric rating scale NRS, with a measurement score from 0 to 10 points. All groups showed decreasing mean perineum pain score at two hours after delivery (before intervention) and after intervention at 24, 48, and 72 hours after delivery that were significantly different at 24, 48, and 72 hours in favor of the ginger extract with $p<0.05$ as shown in Table 3 and Figure 2. For uterine pain score, all groups also showed decreasing over time, but they were not significantly different among groups across all time points with $p>0.05$ as shown in Table 3 and Figure 3.

Adverse drug reactions

No adverse drug reactions were reported or detected at 24 and 48 hours after delivery.

Discussion

In the present study, the authors have shown that

Table 2. Maternal clinical data two hours after delivery and newborn data

Maternal clinical data	Population group			p-value
	Ginger extract (n=33)	Placebo (n=33)	SSD (n=33)	
Temperature (°C); median (min, max)	36.80 (36.60, 37.00)	36.70 (36.50, 36.90)	36.80 (36.50, 37.20)	0.623[a]
Pulse (bpm); median (min, max)	86 (80, 92)	82 (76, 88)	86 (76, 96)	0.549[a]
Systolic blood pressure (mmHg); median (min, max)	120 (115, 130)	120 (110,120)	120 (110,120)	0.235[a]
Diastolic blood pressure; median (min, max)	70 (60, 80)	70 (60, 78)	72 (65, 80)	0.375[a]
Blood loss (mL); median (min, max)	100 (100, 200)	150 (100, 200)	150 (100, 300)	0.160[a]
Level of feeling: feel good; n (%)	33 (100)	33 (100)	33 (100)	1.000[b]
Uterine contraction: normal; n (%)	33 (100)	33 (100)	33 (100)	1.000[b]
Vaginal bleeding: normal; n (%)	33 (100)	33 (100)	33 (100)	1.000[b]
Perineum wound; n (%)				0.172[b]
Normal	33 (100)	30 (90.90)	32 (97.00)	
Oedema	-	3 (9.10)	-	
Other	-	-	1 (3.00)	
Paracetamol 500 mg; n (%)				1.000[b]
Not received	33 (100)	33 (100)	33 (100)	
Sex of newborn; n (%)				
Male	18 (54.5)	13 (39.4)	15 (45.5)	0.466[b]
Female	15 (45.5)	20 (60.6)	18 (54.5)	
Weight of newborn (g); mean±SD	3,004.55±358.17	2,912.88±399.89	3,025.76±413.06	0.463[c]
Apgar score; median (min, max)				0.316[a]
1 minute	8.78 (5, 9)	8.90 (6, 9)	8.81 (6, 9)	
5 minutes	10 (10, 10)	10 (10, 10)	10 (10, 10)	
Gestation age; median (min, max)	39 (38, 39)	38 (38, 39)	38 (38, 39)	1.000[a]
Type of episiotomy; n (%)				0.138[b]
Median	2 (6.10)	1 (3.00)	-	
Right mediolateral	31 (93.90)	31 (93.90)	31 (93.90)	
Left mediolateral	-	1 (3.00)	2 (6.10)	
Type of perineal trauma; n (%)				0.232[b]
Second degree	31 (93.90)	30 (90.90)	33 (100)	
Third degree	2 (6.10)	3 (9.10)	-	

SSD=standard synthetic drug; SD=standard deviation

[a] Kruskal-Wallis H test; [b] Fisher's exact test; c One-way ANOVA

Table 3. Pain score at specific anatomical locations between groups using steamed ginger extract, placebo and SSD at time 2 hours after delivery (before intervention), 24, 48, 72 hours (after intervention) after delivery

Anatomical part	Before and after delivery (hours)	Steamed ginger extract (n=33) mean±SD	Placebo (n=33) mean±SD	SSD (n=33) mean±SD	p-value[a]
Perineum	2	6.12±0.33	6.33±0.25	6.85±0.32	0.202
	24	3.97±0.22[b]	6.30±0.23	4.58±0.36[b]	<0.001*
	48	2.48±0.18[b]	6.09±0.22	3.15±0.29[b]	<0.001*
	72	1.42±0.16[b,c]	2.61±0.18	2.03±0.21	<0.001*
Uterus	2	2.24±0.49	2.30±0.47	2.67±0.47	0.750
	24	1.85±0.39	1.97±0.41	1.94±0.35	0.959
	48	1.55±0.28	1.61±0.34	1.88±0.31	0.584
	72	1.12±0.22	1.00±0.24	1.12±0.19	0.576

SSD=standard synthetic drug; SD=standard deviation

* p<0.05, statistically significant; [a] Kruskal-Wallis H test; [b] p<0.05, Dunn's post-hoc test compared with the placebo group; [c] p<0.05, Dunn's post-hoc test compared with the SSD group

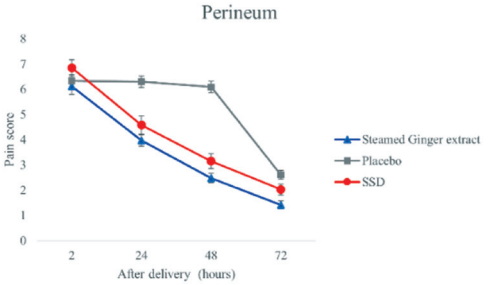

Figure 2. Perineal pain scores at 2 hours after delivery (before intervention) and after intervention at 24, 48, and 72 hours after delivery.

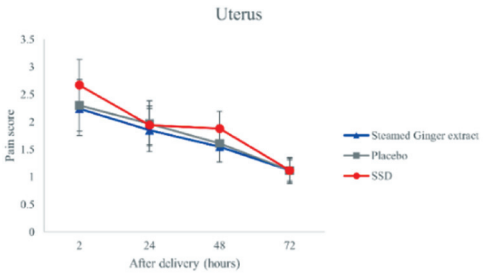

Figure 3. Uterine pain scores at 2 hours after delivery (before intervention) and after intervention at 24, 48, and 72 hours after delivery.

the ethanolic extract of ginger capsule was effective in treating perineal pain compared to placebo and paracetamol. Ginger extract group had lowest score for perineum pain of all groups and no adverse drug reactions. The results from the present study suggest that ginger can be helpful to relieve perineal pain of the first normal postpartum women. Perineal pain is common in postpartum women and often results from episiotomies. It may lead to loss of mobility and discomfort in carrying out daily activities such as caring for the newborn and breastfeeding. Paracetamol is a standard analgesic that is to relieve perineum pain and inflammation in postpartum women and generally effective and well tolerated. Ginger is used in Thai traditional medicine to promote breast feeding, early ambulation, and pain management after delivery. Gingerol and shogaols are the active compounds in the ginger rhizome and both inhibit PGE_2, which is important in the pathogenesis of pain. Ginger that has been heated to 121°C (autoclave) before drug preparation has greater inhibitory activity compared to unheated ginger[5]. Cheng et al. demonstrated improved anticancer potential in vitro of steamed ginger. Gingerol and shogaols exhibit DPPH scavenging activity[6,13] and stimulate blood circulation[6]. These properties contribute to reducing inflammation and pain and promote wound healing in postpartum women. For pain relief, the present study was similar to several studies that have demonstrated the ginger has beneficial effects to act as an inhibitor on cyclooxygenase (COX)[14], resulting in an effective and safe therapy for relieving pain in women with primary dysmenorrhea if administered at the onset or during the three days prior to menstruation[15]. By contrast, paracetamol has more complicated mechanisms of action involving the inhibition of prostaglandin synthesis, serotonin pathway activation, and endocannabinoid enhancement to produce its analgesic effects[16]. Although the authors showed a significant difference each active drug compared to placebo, the mean pain scores between ginger and paracetamol were similar and a lack of difference may be partially explained by the present study small sample size. Nevertheless, large trials will be needed to directly compare their analgesic efficacy and detect differences in tolerability. Ginger capsules appeared to be very well tolerated and no adverse drug reactions, but more preclinical and clinical data are needed to develop the capsules to the international standards for use in patients.

Conclusion

The authors' small study suggests ginger capsules of the ethanolic extract of steamed ginger is effective in postpartum pain relief and was well tolerated. Larger studies are needed to confirm these findings. Nevertheless, the promising results are justified to additional development work with a view to eventual registration.

What is already known on this topic?

In Thai traditional scripture for women's health, ginger (*Zingiber officinale* Roscoe) is widely used for several clinical indications, including postpartum pain, nausea and vomiting due to motion sickness and to promote early ambulation and breast feeding. Thai traditional practitioners always steamed the ginger rhizome before drug preparation as extracted according to local wisdom of Thai traditional practitioners. Previous research has shown the biological activity of steamed and non-steamed ginger rhizomes as follow, the steaming ginger extracts increases antioxidant potency more than non-steamed ginger rhizomes. In addition, the steaming ginger extracts also has a high phenolic content, has an inhibition effect on PGE_2, and NO release with IC_{50} value of 0.40±0.06 µg/mL and 13.47±0.20 µg/mL, respectively. Both inflammatory mediators are

implicated in the pathogenesis of pain. By HPLC analysis, 6-gingerol and 6-shogaol were the main compounds detected in the 95% ethanol extract of steamed ginger and it has been shown that 6-gingerol and 6-shogaol have antioxidant, anti-inflammatory, and antibacterial properties. For this reason, the steaming ginger extracts shows the potential for development of a Thai traditional drug from steamed ginger.

What this study adds?

This study showed significant differences between the three groups ($p<0.05$). Specifically, mean levels of perineum pain score in the steamed ginger extract group were more effective than the SSD and the placebo group at 2, 24, 48, and 72 hours after delivery. The steamed ginger extract exhibited the best activity for reducing perineum pain when compared with placebo and SSD. There was no adverse drug reaction in the steamed ginger extract group. The application of steamed ginger extract for perineum pain relief may be more effective than the SSD for routine postpartum analgesia and having no adverse reactions.

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Conflicts of interest

The authors have no conflict of interest.

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