

**ORIGINAL ARTICLE**

**Effect bromelain and vitamin C on episiotomy wound healing**

*Bromelain and vitamin C on episiotomy wound healing*

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**ABSTRACT**

**Objective.** The purpose of this clinical trial study was to investigate the clinical efficacy of bromelain and vitamin C in reducing pain and improving episiotomy wound healing in primiparous women.

**Materials and Methods.** In this clinical trial, 140 primiparous pregnant women were randomly divided into four groups: bromelain 500 mg three times a day, bromelain combined with oral vitamin C 1000 mg, vitamin C alone, or placebo. The first dose of the drug was administered 2 hours after delivery. The improvement of the wound was measured using the REEDA scale on days 3, 7, and 14 after delivery. Pain intensity was assessed using the Visual Analog Scale (VAS) at 2 hours postpartum, within the first 24 hours after delivery, and 1 hour after drug administration within the first 24 hours after delivery.

**Results.** By the end of the study, 32 patients were available in the bromelain group, 33 in the bromelain and vitamin C group, 32 in the vitamin C group, and 31 in the placebo group. All four study groups showed no significant differences in demographic and obstetric characteristics. The highest degree of wound improvement was observed in individuals receiving bromelain and vitamin C, with a mean wound healing score of  $0.7 \pm 0.6$ , followed by bromelain alone ( $1.3 \pm 0.6$ ), vitamin C alone ( $1.5 \pm 0.8$ ), and placebo ( $1.9 \pm 0.8$ ) ( $P < 0.001$ ). Conversely, the lowest pain levels were reported in the same order: bromelain recipients (mean VAS score:  $2.0 \pm 0.5$ ), bromelain and vitamin C recipients ( $2.0 \pm 0.6$ ), vitamin C recipients ( $2.3 \pm 0.4$ ), and placebo recipients ( $2.6 \pm 0.5$ ) ( $P < 0.001$ ).

**Conclusions.** In primiparous women, the combination of bromelain and vitamin C effectively improves episiotomy wound healing and reduces pain.

### **Key words**

Episiotomy; bromelain; vitamin C, pain.

### **Introduction**

Episiotomy, which refers to a perineal incision, is performed to facilitate childbirth and prevent fetal distress [1]. This surgical procedure is more common in primiparous women due to greater tissue resistance [2,3]. In Asian countries, the prevalence of episiotomy is notably high. For instance, in India during 2007-2008, nearly 70% of women underwent episiotomy, while in Thailand in 2005, over 90% of women had the procedure[4]. A study conducted in Shahroud (Iran) in 2015 reported a prevalence rate of 5.41% [5]. Although episiotomy wounds tend to heal well due to adequate blood supply in the area, they can be delayed in healing due to contamination from vaginal secretions, urine, feces, and a moist environment [6]. The REEDA score is a standardized tool used to assess the healing process of episiotomy wounds. It evaluates five key components: Redness, Edema, Ecchymosis, Discharge, and Approximation of the wound edges[7] Improper care of episiotomy wounds can lead to short-term complications such as infection, pain, discomfort during intercourse, and long-term complications like perineal tears in subsequent deliveries [8]. Various drugs and different care approaches have been recommended to improve wound healing and reduce pain in these patients [9]. Notably, the use of herbal remedies is acceptable, especially for breastfeeding mothers who do not require interference with lactation.

Bromelain, a proteolytic enzyme derived from pineapples, has been studied for its potential benefits in wound healing. The fibrinolytic activity of bromelain has been attributed to enhanced conversion of plasminogen to plasmin. By means of these reactions, vascular permeability may be enhanced and edematous fluid may be absorbed by tissue[10]. Commercially available bromelain is derived from the stems of pineapple plants[11]. When ingested, bromelain dose-dependently reduces plasma bradykinin levels and increases prostacyclin, thromboxane A<sub>2</sub>, and prostaglandin E<sub>2</sub> in inflammatory areas [11]. These effects can lead to inflammation reduction and wound improvement[12]. Studies have demonstrated that bromelain is well-tolerated and does not have serious side effects [13].

Vitamin C, also known as ascorbic acid, is the most effective water-soluble antioxidant. Its natural concentration in human blood plasma ranges from 0.6 to 1.8 milligrams per liter. Vitamin C solution stimulates collagen synthesis without affecting the synthesis of other proteins [14]. Additionally, it is essential for prolyl hydroxylase, which contributes to collagen stability. Furthermore, vitamin C is necessary for lateral cross-linking of collagen molecules, providing tissue strength. Ultimately, by stimulating collagen gene expression, it contributes to wound improvement [15]. Research findings indicate that vitamin C plays a role in all stages of wound healing, including the inflammatory phase, where it is required for neutrophil apoptosis and clearance [16].

In some clinical trials, bromelain has been shown to reduce pain and improve wound healing in women who have undergone episiotomy [13,17]. However, the results of these studies are controversial and limited. Most studies investigating the impact of bromelain on episiotomy wound healing have been conducted with small sample sizes. Nevertheless, the combined effect of bromelain and vitamin C on wound improvement and pain reduction in these

patients remains unexplored. Therefore, this clinical trial aimed to assess the effect of bromelain in conjunction with vitamin C on the healing of episiotomy wounds in primiparous women.

## **Materials and Methods**

This clinical trial was conducted at Hamedan University of Medical Sciences. The ethics committee of Hamedan University of Medical Sciences approved the study with the identifier IR.UMSHA.REC.1401.411, and it was also registered in the Iranian Clinical Trials Registry (IRCT20160523028008N25). Demographic information (age and BMI), educational level, place of residence (urban or rural), gestational age, cervical dilation at admission, duration of rupture of membranes until delivery, duration of the first and second stages of labor, and neonatal weight were collected from patients' records.

After achieving complete cervical dilation and identifying a 3 to 4 centimeter diameter from the fetal head's crowning, a midline episiotomy was performed by trained individuals under the supervision of obstetric surgeons. Suture material used was Chromic catgut 2-0(SUPA, company, Iran). The duration of episiotomy repair and the size of the incision will be recorded. The first dose of medication or placebo was administered to the participants under the researcher's supervision, at least 2 hours after episiotomy repair. Participants are advised to take the medication or placebo one hour before or two hours after meals, three times a day for one week. The improvement of the wound will be assessed using the REEDA scale [18] in the lithotomy position, with examination performed by the researcher using a light source. Patients were instructed to follow several guidelines to preserve the episiotomy shape and promote healing. They were advised to keep the episiotomy site clean and dry by washing the area with warm water and mild soap, and gently patting it dry. Cold compresses were recommended to reduce swelling and discomfort, while sitz baths with warm water were encouraged to promote healing and alleviate pain. Patients were instructed to avoid heavy lifting and strenuous activities to prevent strain on the perineal area. A high-fiber diet and adequate fluid intake were recommended to prevent constipation and reduce strain during bowel movements. Regular follow-up visits were scheduled to monitor healing and address any complications. Acetaminophen was administered to patients based on their reported pain levels, following a standardized pain management protocol. The criteria for using acetaminophen included a pain score of 4 or higher on a 10-point visual analog scale (VAS). Pain assessments were conducted every 4 hours, and acetaminophen was given as needed to manage moderate to severe pain.

### **Inclusion Criteria:**

- Age between 18 and 40 years.
- Gestational age between 37 and 42 completed weeks.
- Singleton pregnancy.
- Cephalic presentation.
- Vaginal delivery.
- Newborn weight between 2500 and 4000 grams.
- Midline mediolateral episiotomy with a length of 3-4 centimeters.
- Minimum education level of fifth grade.

- BMI within the range of 19-26(Kg/m<sup>2</sup>).
- Cervical dilation of 3-5 centimeters.

**Exclusion Criteria:**

- Presence of debilitating wound healing diseases (such as diabetes, renal disorders, anemia, liver conditions, cystocele, and excessive anxiety).
- Use of narcotics and tobacco.
- Administration of wound healing medications (including glucocorticoids, anticoagulants, immunosuppressants, antibiotics, and chemotherapy).
- Manual extraction of the placenta.
- Curettage performed within the first 24 hours after delivery.
- Early rupture of membranes.
- Signs suggestive of infection, anemia, perineal and vaginal injuries.
- Abnormal postpartum bleeding.
- Formation of hematoma during episiotomy repair.
- Neonatal anomalies.
- Stillbirth.
- Abnormal duration of the first, second, and third stages after delivery.
- Vaginal tears and extension of episiotomy.
- Use of vacuum-assisted delivery

**Intervention:**

1. Bromelain Group: Participants were given a 500-milligram dose of bromelain, administered 2 hours after delivery. They continued this regimen three times a day for 7 days postpartum.
2. Bromelain & Vitamin C Group: Similar to the first group, participants received 500 milligrams of bromelain shortly after delivery. Additionally, they took a daily 1000-milligram vitamin C tablet for 7 days postpartum.
3. Vitamin Group: Participants in this group orally consumed 1000 milligrams of vitamin C daily for 7 days.
4. Placebo Group: Administered within 2 hours after delivery, the placebo group followed a placebo treatment three times a day for 7 days

**Outcome:**

Pain intensity Assessed using the Visual Analog Scale (VAS) at 2 hours after delivery, before medication administration, and at 1 hour after medication administration during the first 24 hours postpartum. Wound healing REEDA on the 3rd, 7th, and 14th days following delivery.

As previously described, this scale assesses various aspects of mental and emotional well-being during the past week, providing valuable insights into postpartum health[18].

**Randomization:** Randomization was performed using a table of random numbers ranging from 1 to 140. The groups were allocated as follows:

- Groups 1-35: Placebo.
- Groups 36-70: Vitamin C.
- Groups 71-105: Bromelain.
- Groups 106-140: Combination of Vitamin C and Bromelain.

**Blinding:** In this study, the distinction between drug and placebo was not discernible. Both drug and placebo were coded by the pharmacist as categories one, two, or three. Therefore, the study was conducted in a blinded manner. (Starch capsules were used as the placebo in this study).

### **Sample Size & Statistically analyze**

Sample Size Based on the Findings of the Study by Golzar and Colleagues in the intervention group, the wound healing rate was estimated to be 51.2%, while in the control group, it was 19.5% with a statistical power of 80% and a Type I error of 0.05. In this study, data analysis was performed using SPSS version 20. For descriptive statistics, the mean and standard deviation were used to describe and report quantitative variables with a normal distribution, while the median and interquartile range were employed for non-normally distributed variables. Qualitative variables were expressed in terms of ratios and percentages. To examine quantitative variables between two groups, an independent t-test was used if the normality assumption was met. In case of non-normality, the non-parametric equivalent, the Mann-Whitney U test, was utilized. For comparing nominal qualitative variables between two groups, the Chi-square test was employed. When analyzing quantitative variables measured more than twice, the repeated measures analysis of variance (ANOVA) was applied. A significance level of 5% was considered for all statistical tests.

### **Results**

In total, 12 patients were excluded during the study follow-up period due to not following up for assessing the intended outcomes. Specifically, 3 patients were from the Bromelain group, 2 patients from the Bromelain and Vitamin C group, 3 patients from the Vitamin C group, and 4 patients from the placebo group (Figure1).

Regarding demographic characteristics, pre-pregnancy body mass index (BMI), neonatal birth weight, gestational age, stages of labor, and the number of sutures, there were no statistically significant differences among the four study groups, additional details are displayed in table1

The wound healing improved in all four groups over time. The repeated measures analysis of variance demonstrated that the wound improvement was statistically significant within all groups (within-group comparison). Furthermore, there was a statistically significant difference between the groups, with the highest degree of improvement observed in the order of patients receiving Bromelain and Vitamin C, Bromelain, Vitamin C, and placebo(table2).

In terms of pain severity, all four study groups had similar average pain levels before drug consumption. However, over time, the pain intensity decreased in each of the four study groups. The repeated measures analysis of variance revealed that the reduction in pain was statistically significant within all groups (within-group comparison). Additionally, there was a statistically significant difference between the groups, with the lowest pain levels observed in the following order: patients receiving Bromelain, Bromelain and Vitamin C, Vitamin C, and placebo (table 3).

Patients who received bromelain and vitamin C had a lower intake of acetaminophen compared to those who received a placebo. Although patients in the placebo group required more analgesics, the difference between the groups was not statistically significant. (table 4).

## Discussion

The findings of the current study indicate that combining bromelain with vitamin C can accelerate wound healing in primiparous women compared to using bromelain or vitamin C alone and the placebo. However, the reduction in pain experienced by these patients who received bromelain along with vitamin C was comparable to those who received bromelain alone, but less than those who received the placebo.

Previous research also suggests that the use of bromelain, whether in the form of topical ointment, fruit extract, or oral supplementation, is effective in accelerating wound healing, including episiotomy [19,9]. For instance, a study conducted by Golzar and colleagues in [13] involved 82 primiparous women who received 100 mg of bromelain or the placebo three times a day for up to 6 days after childbirth. Their findings revealed that the average wound improvement scores in the bromelain group were lower compared to the placebo group on the third, seventh, and fourteenth days after delivery. In a study conducted by Gaikwad and colleagues [20] in 2019, it was demonstrated that among 60 primiparous women, 30 of whom used pineapple extract, there was a significant difference in the RIDA scale between the intervention group and the control group ( $5.13 \pm 0.97$  vs.  $7.83 \pm 0.79$ ,  $P=0.000$ ). Another study by Umamy and colleagues [9] also showed that consuming pineapple fruit juice accelerates the healing process of episiotomy wounds compared to the control group, with a significant difference. Other studies, including Soheilifar et al.'s study in [21], found that oral bromelain at a dose of 500 milligrams per day can be an effective treatment for reducing pain in the graft area after free gingival graft surgery and may also contribute to wound healing in the donor site. In a study conducted by Baumuller [22] a controlled double-blind trial was performed on patients with exercise-related foot injuries. Patients treated with oral bromelain showed faster improvement compared to the placebo group. Zareandi et al [17] also reported that consuming 500 milligrams of bromelain capsules twice daily is a suitable alternative to oral antibiotics for patients with chronic periodontitis, which has wound healing properties. Bromelain, found in pineapples, acts as an anti-inflammatory agent and may reduce the average days of pain and wound healing, including episiotomy wounds [23].

However, the results of Howat and Lewis study [24] on the effect of bromelain in improving wounds after mediolateral episiotomy in primiparous women showed that the return of edema and redness up to the sixth day postpartum was faster in individuals receiving bromelain, especially those with severe inflammation in the area, compared to the placebo group. Nevertheless, this difference was not statistically significant, possibly due to different dosages compared to the present study. In contrast, Cowie and colleagues [25] demonstrated in a study that preoperative consumption of 40 milligrams of bromelain four

times a day for vaginal plastic surgery had positive effects in reducing edema, hematoma, and vaginal secretions on days 5 and 14 postoperatively.

In relation to the impact of bromelain on pain reduction, research results also suggest that this supplement can be effective in reducing pain in patients with episiotomy. For example, a study conducted by Golzar [13] demonstrated that bromelain consumption significantly reduces pain in these patients. Findings from the study by Howat and colleague [24] indicated that bromelain is effective in pain relief for patients undergoing episiotomy surgery, although statistically, this reduction was not significant compared to the control group. This lack of significance may be due to the lower dosage used in these patients. Ezeome and colleague [26] showed that the combination of bromelain and trypsin is effective in pain reduction after laparotomy. Similarly, studies by Majid and colleagues [27], Zatusni and colleagues [19], and Walker and colleagues [28] have also confirmed the analgesic effect of bromelain. However, a study by Eslami and colleagues [29] revealed that bromelain consumption at a dose of 200 milligrams four times a day after dental surgery does not have a significant analgesic effect. The findings of this study demonstrated that patients who received bromelain had lower pain medication usage compared to those who did not receive this drug. However, their difference was not statistically significant, possibly due to the small sample size of the individuals examined. The results of the study by Golzar and colleagues also support the findings of the present study [13].

In recent years, significant advancements have been made in pain management during labor and cesarean sections. For instance, the efficacy of single wound infiltration with bupivacaine and adrenaline during cesarean delivery has been demonstrated to significantly reduce postoperative pain and opioid use [30]. Additionally, the use of hyoscine butyl-bromide has been shown to shorten the active phase of labor, thereby potentially reducing the overall pain experienced by patients [31]. Furthermore, hyaluronidase injections have been explored for their potential to reduce perineal trauma during vaginal births, although the evidence remains inconclusive [32]. Various perineal techniques, such as massage and warm compresses, have also been studied for their effectiveness in reducing perineal trauma and postpartum complications, highlighting the need for further research in this area [33].

Vitamin C is one of the essential vitamins for humans, which the body is unable to produce on its own. Findings from this study indicate that adding vitamin C to bromelain can enhance wound healing speed [34]. Other studies have also demonstrated that vitamin C consumption can be effective in accelerating wound recovery [35]. In a meta-analysis study published by Thevi and colleagues [36] shown that vitamin C supplementation increases wound healing speed by 3.94 times compared to a placebo (with an odds ratio of 3.99 and a 95% confidence interval from 2.06 to 7.73), although statistically, this difference was not significant. Another meta-analysis study, which reviewed the results of 18 studies, highlighted the effectiveness of vitamin C, especially in improving intestinal wound healing [16].

In the present study, we did not observe any side effects following bromelain consumption. Previous studies also suggest that bromelain is not associated with serious side effects [13,20]. However, some mild side effects, such as gastrointestinal discomfort, have been reported. According to the FDA, bromelain is an approved supplement. It is recommended that pregnant women and patients with a history of liver or kidney disease avoid its use.

## Conclusions

In primiparous women, the combination of bromelain and vitamin C is effective in wound healing and reducing pain after episiotomy . However, larger sample studies are necessary to confirm the results of this study.

## COMPLIANCE WITH ETHICAL STANDARDS

**Authors' contribution:** SH: reviewed and edited the manuscript, conceptualized and designed the study, FS: collaborated on the analysis, MS: critically reviewed the manuscript, and conceptualized and designed the study. All authors reviewed the manuscript and they agree with the final version

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## Study registration

This study registered in the Iranian Clinical Trials Registry (IRCT20160523028008N25).

## Disclosure of interests

The authors declare no competing interests

## Ethical approval

Hamadan University of Medical Sciences (IR.UMSHA.REC. 1401.411)

## Informed consent

Consent to participate from all patients was obtained.

## Data sharing

Data are available under reasonable request to the corresponding author.

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Table1: Comparison of demographic and midwifery characteristics of patients in treatment groups

Variable		Bromelain , n=32	Bromelain& Vitamin C ,n=33	Vitamin C , n=32	Placebo , n=31	P
Age(yr.), Mean ± SD		25.9±4.4	25.8±4.4	26.1±4.0	25.9±4.7	0.958*
BMI (kg/m <sup>2</sup> ), Mean ± SD		26.0±2.4	26.0±1.8	25.1±1.9	25.2±2.0	0.284*
Berith weight (gr), Mean ± SD		3020.3±308.2	3075.7±343.5	3026.0±304.0	3059.7±294.5	0.912*
Gestational age(week), Mean ± SD		37.8 ± 1.0	37.4±0.9	37.6±1.1	37.5±0.9	0.513*
Cervical dilatation (cm), Mean ± SD		3.0±0.9	2.9±0.9	3.2±1.1	2.3±0.8	0.509*
Time of first labor stages (hour), Meen± SD		7.6±2.9	8.0±2.9	8.1±3.1	7.4±2.7	0.754*
Time of second labor stages (min), Mean ± SD		41.1±16.1	39.7±15.6	38.6±14.5	37.9±15.8	0.754*
Time of rupture of membrane until delivery (hour), Mean ± SD		6.0±2.9	6.0±3.0	6.1±3.2	6.0±3.3	0.998*
Sutures (number of stitches), Mean ± SD		7.6±1.6	7.8±1.6	7.7±1.6	7.9±7.7	0.823*
Resident	Urban	21 (65.6)	20 (60.6)	19 (59.4)	21 (67.7)	0.884#
	Rural	11 (34.4)	13 (39.4)	13 (40.6)	10 (32.3)	
Education	Under diploma	8(25.0)	6 (18.2)	6 (18.7)	4 (13.3)	0.952#
	Diploma	18 (56.3)	21 (63.6)	19 (59.4)	19 (63.3)	
	Academic	6 (18.7)	6 (18.2)	7 (21.9)	7 (23.3)	

Note: \*Analysis of variance (ANOVA), #: Chi2, SD: Standard deviation, BMI: body mass index, CM: centimeter, min: minutes

Table2: Evaluation of wound healing progression in follow-up among study groups

Group		Time ((Mean ± SD)			P (Repeated measures ANOVA)		
		3days after delivery	7 days after delivery	14 days after delivery	Time	group	Time/group
Bromela in	Total	4.0 ± 0.7	2.6 ± 0.6	1.3±0.6			
	Redness	0.7±0.4	0.5 ±0.3	0.1 ±0.2			
	Edema	0.9±0.5	0.6 ±0.2	0.3±0.2			
	Ecchymosis	0.8±0.6	0.6±0.2	0.4. ±0.2			
	Discharge	0.8±0.5	0.4±0.3	0.2±0.2			
	Approximation	0.7±0.4	0.6±0.4	0.2±0.2			
Bromela in& Vitamin C	Total	3.6±0.6	2.3±0.6	0.7±0.6			
	Redness	0.6 ±0.2	0.4±0.3	0.1±0.2			
	Edema	0.8±0.5	0.5±0.2	0.2 ±0.2			
	Ecchymosis	0.9±0.6	0.7±0.3	0.2±0.2			
	Discharge	0.7±0.4	0.3±0.3	0.1±0.2			
	Approximation	0.6±0.4	0.3±0.3	0.1±0.2	<0.001	<0.001	<0.001
Vitamin C	Total	4.0±0.6	2.7 ± 0.6	1.5 ±0.5			
	Redness	0.7 ±0.3	0.6±0.3	0.2±0.3			
	Edema	0.8±0.5	0.6±0.2	0.3 ±0.2			
	Ecchymosis	0.8 ±0.6	0.6±0.2	0.3±0.2			
	Discharge	1.0±0.05	0.4±0.2	0.3±0.2			
	Approximation	0.7±0.5	0.6±0.2	0.3±0.2			
Placebo	Total	4.2±0.7	3.2 ± 0.6	1.9 ± 0.8			
	Redness	0.8±0.5	0.8±0.3	0.3±0.3			
	Edema	1.0±0.6	0.6±0.2	0.4±0.2			
	Ecchymosis	0.9±0.6	0.7±0.3	0.2±0.2			
	Discharge	0.9±0.5	0.6±0.2	0.5±0.3			
	Approximation	0.8±0.7	0.7±0.3	0.4±0.2			

Table3: Evaluation of pain intensity in patients based on the type of intervention

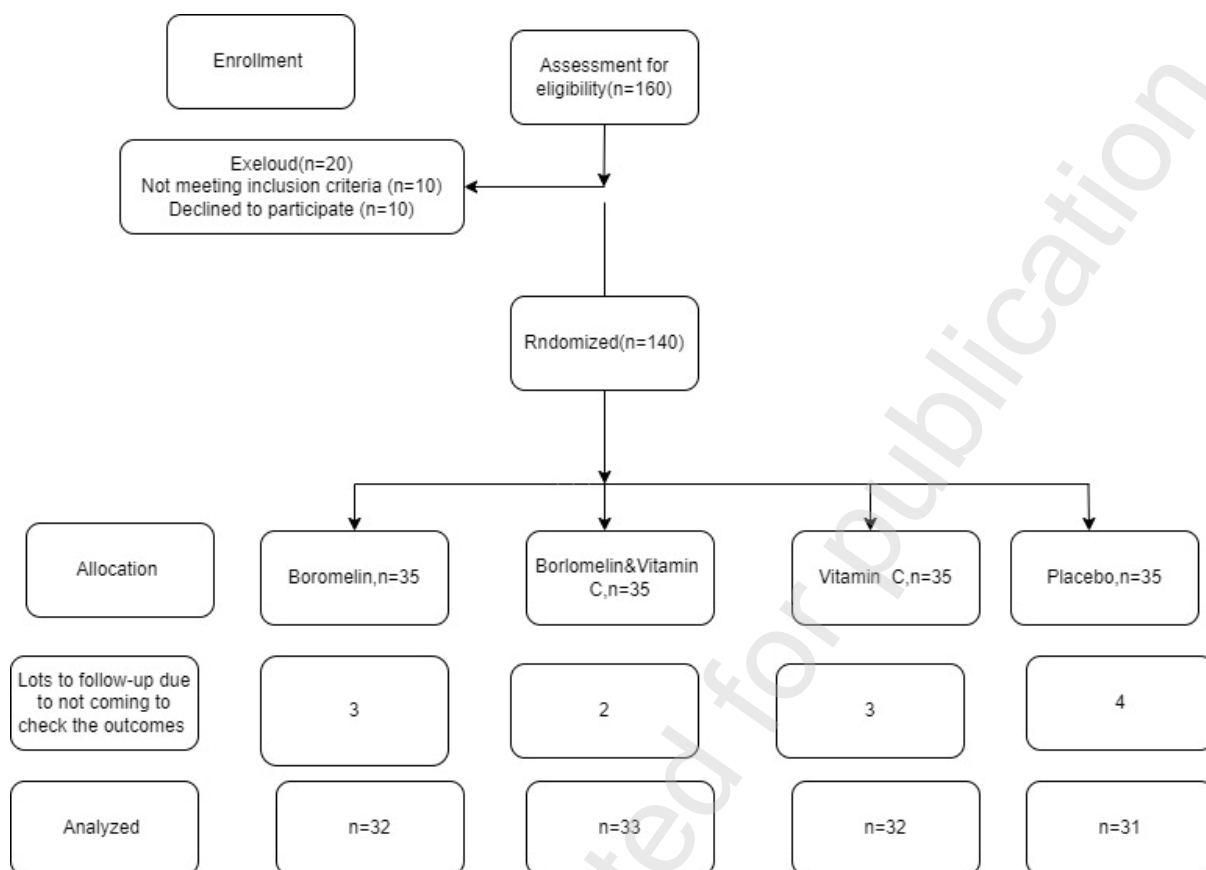
Group	Time ((Mean ± SD)			<i>P</i> (Repeated measures ANOVA)		
	2hour after delivery	One hour after drug	24 hours after delivery	Time	group	Time/group
Bromelain	5.0 ± 0.6	3.3 ± 0.8	2.0±0.6	<0.001	<0.001	<0.001
Bromelain& Vitamin C	4.8±0.9	3.4±0.5	2.0±0.5			
Vitamin C	5.0±0.7	4.3 ± 0.6	2.3 ±0.4			
Placebo	4.8±0.8	4.0 ± 0.5	2.6 ± 0.5			

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Table 4: Acetaminophen was given to participants in both the international groups and the placebo group

Acetaminophen	Bromelain	Bromelain& Vitamin C	Vitamin C	Placebo	P(chi2)
	frequency (%)	frequency (%)	frequency (%)	frequency (%)	
Yes	13 (40.6)	13 (39.4)	19 (59.4)	19 (61.3)	0.150
No	19 (59.4)	20 (60.6)	13 (40.6)	12 (38.7)	
Total	32 (100.0)	33 (100.0)	32 (100.0)	31 (100.0)	

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**Figure 1:** Participant flowchart for the intervention study in participants.