**Ananas comosus** Effect on Perineal Pain and Wound Healing After Episiotomy: A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract

**Background:** *Ananas comosus* has long been used for medical purposes. Currently, we are experiencing an unprecedented interest in the use of complementary medicine as well as a growing attention to traditional products such as bromelain for wound healing and reducing pain.

**Objectives:** The aim of this study was to determine the effect of oral bromelain on perineal pain and wound healing after episiotomy in primiparous women.

**Patients and Methods:** In this double-blind placebo-controlled clinical trial, 82 primiparous women fulfilling the inclusion criteria received bromelain or placebo randomly. Participants were given three tablets, three times a day for six successive days. The initial dose was given 2 hours after delivery. Episiotomy pain was measured using VAS scale before the initial dose, as well as on the 1st hour and on the 3rd, 7th and 14th days after the initial dose. Wound healing was measured using REEDA scale on the 3rd, 7th and 14th days after delivery.

**Results:** Episiotomy pain significantly reduced in bromelain group compared with the placebo group (P < 0.05) and wound healing was faster in bromelain group compared with the placebo group (P < 0.05) on follow-up days.

**Conclusions:** The results showed the effectiveness of bromelain on episiotomy pain and wound healing. Therefore, it is suggested to use bromelain in postoperative stage to improve wound healing and reduce pain.

**Keywords:** Bromelains, Pain, Episiotomy, Wound Healing

1. Background

Episiotomy is an incision made in the perineum during a vaginal delivery to facilitate and expedite delivery and prevent perineal split (1). Episiotomy is the most common surgical incision of the perineum among obstetrical procedures (2). Pain of episiotomy is a significant morbidity in the puerperium (3). Episiotomy, like other incisions, has risks and complications (1, 4). Long-term pain, delayed wound healing and this mutual relationship continues if there is no treatment. The delay in perineal wound healing leads to bad anatomical outcomes (5). Therefore, having in mind the physiological and psychological consequences, effective treatment is crucial both from patient’s and economical viewpoints (6).

Synthetic drugs, despite their efficiency, have many adverse effects (5). Recently, interest in the use of complementary medicine has increased; besides, there is a growing attention to traditional products such as bromelain for wound healing and reducing pain (7).

*Ananas comosus* (pineapple) has long been used for medical purposes. Native cultures used it as a digestive aid and a remedy for skin disorders. Bromelain is a crude, aqueous extract derived from pineapple stems and fruits. There are four distinct proteases in pineapples; the two major enzymes are now described as stem bromelain and fruit bromelain. Several additional components have been found in bromelain, including peroxidase, acid phosphatase, several protease inhibitors and organically bound calcium (2). In recent studies a wide range of therapeutic benefits have been suggested for bromelain, such as anti-inflammatory, anti-edematous, reducing pain, wound healing, anticoagulant, etc. (2, 8).

Many studies suggest that the proteolytic component of bromelain is responsible for the pharmacological effects (2, 8, 9). Up to now, several possible mechanisms have been proposed for antiedematous, anti-inflammatory, fibrinolytic and analgesic efficiency of bromelain. Experiments demonstrate that bromelain decreases the plasmakinin level. Similarly, bromelain causes a dose dependent decrease of bradykinin levels at inflammatory sites and a parallel decrease of prekallikrein levels in serum (8). Studies of acute inflammation have shown that bromelain reduces the level of PGE₂ and Tromboxan B₂ dose-dependently (8, 10). 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 tissues (8, 9).

Zatuchni and Colombi (1967), in a double blind controlled trial, stated that patients who received bromelain treatment experienced significant decrease of pain associated with mediolateral episiotomy (11).

Cowie et al. (12) and Howat and Lews (13) showed that bromelain has no effect on perineal pain and wound healing. Brown et al. (7) and Emmanuel and Aloy showed the effectiveness of combination of bromelain on speeding up wound healing and reducing pain (14).

Recently, interest in the use of complementary medicine has increased; besides, there is a growing attention to traditional products such as bromelain for wound healing and reducing pain (7).

2. Objectives

This was a randomized double blind controlled study performed to determine the effect of bromelain on post-episiotomy pain and wound healing in primiparous women.

3. Patients and Methods

This was a single-center randomized, double-blind, placebo-controlled two-week trial approved by the institutional ethics committee of Ahvaz Jundishapur university of medical sciences and registered in the Iranian registry of clinical trials (http://irct.ir) under the IRCT No.: IRCT138810112952N1. The trial was conducted at Amiralmomenin hospital of Ahvaz, Iran, between June and October 2009. The sample size for the experimental and control groups was determined as 40 persons per group after the pilot study.

Primiparous women admitted to delivery unit in Amiralmomenin hospital, Ahvaz, Iran, were evaluated in this study. Including criteria were age between 18 - 35 years, gestational age between 37 - 42 weeks, single fetus with cephalic presentation, body mass index of 19.8 - 26, a minimum educational of the fifth grade of elementary school, normal vaginal delivery, cervical dilatation of 2 - 3 cm, mediolateral episiotomy of 3 - 4 cm, newborn weight between 2500 - 4000 grams, Ahvaz resident and Iranian origin. Exclusion criteria were any disease that impaired wound-healing (diabetes, kidney disease, anemia, liver disease, cystocele and over-stress disorder), prolonged labor, anal-sphincter and valve disruption during vaginal delivery, manual placenta removal and courage, PROM (pre labor rupture of membranes), using medicine affecting wound healing (glucocorticoids, antithrombotic drugs, immunosuppressive drugs, antibiotics and chemotherapy drugs) and narcotics, formation of hematoma in episiotomy area, PPH (post-partum hemorrhage), stillbirth and newborn anomalies.

3.1. Intervention

Each Bromelain Tablet was made from 100 mg bromelain obtained from powder content of bromelain capsules, pineapple source, 500 mg, Natural Factors Company, Canada with diluting capsule contents with wheat flour and rheological properties adjusted with magnesium stearate as lubricant. Each gram of Bromelain extract contains 1000GDU (gelatin digesting units) and 1500 MCU (milk clotting units) of enzyme activity. Bromelain and placebo tablets were made at the faculty of pharmacy, Ahvaz Jundishapur university of medical sciences.

The tablet packages were randomly coded numerically using block randomization method (block size = 4). The researcher and patients were all blind, not aware of the content of packages. Three tablets were given three times a day for six successive days. Patients were recommended to consume tablets at least one hour before a meal or two hours after a meal. The initial dose was administered two hours after delivery. All the research units were told that they could use Acetaminophen in case of failure in reduction of pain. The researcher contacted participants the night before the appointment as a reminder. All the participants were given a phone number so that they could consult the researcher if they faced any possible problems. The researcher also checked the number of pills taken by participants during each visit.

3.2. Outcome Measures

All the research stages were performed by a single researcher. After labor of fetus and placenta, the size of the episiotomy cut through the most internal section was measured using a sterile swap and a ruler as well as chromatic catgut 2 - 0 suture according to the routine method (1). The duration of episiotomy healing from the beginning of healing as well as the number of skin stitches were recorded. After at least two hours after episiotomy healing and fading of the lidocaine effect, pain was measured and the first dose of medication was administered.

Pain score was assessed by the VAS (visual analog scale) between 0 - 10 according to women's own report where 'zero' shows lack of pain and 'ten' the highest level of pain ever experienced.

Episiotomy pain was measured before the initial dose. Pain was assessed subsequently one hour after the initial dose.

In the days 3, 7 and 14 after labor, the wound healing rate was assessed using REEDA Scale in lithotomy position by the researcher. The REEDA scale includes five variables: redness, edema, erythema, discharge of wound and approximation (closeness of skin edges), with a score of 0 - 3 for each of the parameters to indicate increasing severity of wound complication. This is a healing assessment tool based on a scale of three points. Score 3 is indicative of very poor wound healing. Total score ranged from 0 to 15 points. On the first postpartum day, the score is possible to range from 0 to 3; by the second week postpartum, the score should be 0 to 1(15).

Participants reached the hospital's clinic and examined...
on 3rd, 7th and 14th days after the labor from 8:00 in the morning to 12 at noon. The pain was evaluated only if the participant had not used any sedatives within six hours before reaching the clinic.

Complete remedy of the wound in the episiotomy area and lack of pain in fourteenth day after delivery measured in the two groups. Acetaminophen use during the follow-up was studied as well. The participants were examined for adverse effects of tablets during the follow-up using interviews and observation.

3.3. Statistical Analysis

Data was analyzed using SPSS software version 15. In this study, descriptive statistics were mean, standard deviation and frequency distribution. To compare the groups for quantitative variables, independent t test and chi-square test were used. Student’s t test was used to compare baseline pain score for the study groups. A repeated-measured ANOVA was administered to compare intragroup changes. Dependent variables were VAS as well as wound healing scores. Independent variables were random and fixed effects of the two groups (Bromelain and Placebo), measurement time and their interactions. When a significant F ratio was identified, differences were assessed using a Tukey post hoc test. P value < 0.05 was considered as statistically significant.

4. Results

Flowchart of participants in the study is exhibited in Figure 1. There was no significant deference in demographic details and obstetric information between bromelain and placebo groups (Table 1). The results showed no significant difference between groups in baseline about pain score (P = 0.74) (Table 2).

Results of two-way repeated ANOVA analysis showed no major violation of assumptions of normality and homogeneity of inter-group variance. The repeated-measured ANOVA showed a significant change in VAS during the study period (P < 0.0001).

Total mean for VAS in Bromelain and placebo groups were 3.77 ± 0.13 and 4.12 ± 0.12, respectively. A significant difference in VAS was also seen in both groups (P < 0.04). There was no significant interaction between time and groups (P > 0.64). Pairwise comparisons of the pain score, between times of follow-up is shown in Table 3.

Figure 2 shows the comparison of pain reduction process between bromelain and placebo groups.

The repeated-measured ANOVA showed a significant change in REEDA during the study period (P < 0.00) (Table 4). Figure 3 shows the comparison of wound healing process between bromelain and placebo groups.

Total average REEDA in bromelain and placebo groups were 1.77 ± 0.16 and 2.67 ± 0.16, respectively. A significant difference in REEDA was also seen in both groups (P < 0.00). There was no significant interaction between time and groups (Table 4).

78% of bromelain group had no pain on the 14th day after labor compared with 53.2% of the placebo group (P < 0.02). Furthermore, 51.2% of the bromelain group achieved complete wound healing on day 14 after labor compared with 19.5% of the placebo group (P < 0.003).

| Table 1. Demographic Details and Obstetric Information in the Bromelain and Placebo Groups |
|---------------------------------|----------|----------|--------|
| Demographic Details and the Obstetric Information | Bromelain | Placebo | P Value |
| Age, y | 23.97 ± 3.42 | 23.46 ± 3.82 | .54 |
| Body mass index before pregnancy | 22.53 ± 1.61 | 22.90 ± 1.74 | .96 |
| Gestational age, wk | 39.3 ± 0.89 | 39.3 ± 1 | .93 |
| Cervical dilatation at intervention | 2.8 ± 0.5 | 2.8 ± 0.8 | .2 |
| Length of rupture of membrane until delivery, min | 411.88 ± 276.92 | 365.51 ± 279.75 | .92 |
| Length of labor stages, min | | | |
| First | 437.36 ± 196.32 | 426.17 ± 200 | .67 |
| Second | 37.27 ± 30.25 | 33.61 ± 26.18 | .44 |
| Number of vaginal examinations during labor | 8.59 ± 2.82 | 7.76 ± 2.62 | .76 |
| Length of episiotomy repair, min | 14 ± 4 | 13.29 ± 3.79 | .6 |
| Number of skin sutures | 5.51 ± 1.39 | 5.29 ± 1.15 | .21 |
| Newborn weight, g | 3320 ± 367 | 3265 ± 324 | .5 |

*Data are presented as group (mean ± SD) and n = 41.
Table 2. Pain Score in Baseline of Women in Bromelain and Placebo Groups

| Day                          | Study Group | P Value |
|------------------------------|-------------|---------|
| Before initial dose (baseline) | Bromelain   | 5.9 ± 1.7 |
|                              | Placebo     | 5.7 ± 1.4 |
|                              |             | .74     |

Data are presented as mean ± SD and n = 41.

Table 3. Multiple Comparison of Mean Difference of VAS Pain Score Based on Tukey Post hoc Test

| Time (I) | Time (J) | Mean Difference (I-J) | P Value |
|----------|----------|-----------------------|---------|
| Baseline | After ID | 0.4634                | .473    |
| Baseline | Day 3    | 1.1463                | .001    |
| Baseline | Day 7    | 2.7683                | .0001   |
| Baseline | Day 14   | 5.0512                | .0001   |
| After ID | Day 3    | 0.683                 | .113    |
| After ID | Day 7    | 2.3049                | .0001   |
| After ID | Day 14   | 4.5878                | .0001   |
| Day 3    | Day 7    | 1.6220                | .0001   |
| Day 3    | Day 14   | 3.9048                | .0001   |
| Day 7    | Day 14   | 2.2829                | .0001   |

The mean difference is significant at the 0.05 level.

Table 4. Multiple Comparison of Mean Difference of Wound Healing Score Based on Tukey Post hoc Test

| Time (I) | Time (J) | Mean Difference (I-J) | P Value |
|----------|----------|-----------------------|---------|
| Day 3    | Day 7    | .646                  | .000    |
| Day 3    | Day 14   | 1.9146                | .000    |
| Day 7    | Day 14   | 1.2683                | .000    |

The mean difference is significant at the 0.05 level.

Figure 2. Comparison of Pain Reduction Process Between Bromelain and Placebo Groups

Figure 3. Mean Wound Healing Score for the Two Study Groups in 14-Day Period

5. Discussion

In this trial, reduction in VAS was more in bromelain group compared to the placebo group. Zatuchni and Colombi showed that average of perineal pain in bromelain group was significantly lower than placebo group on 1st, 2nd, 3rd and 4th days after delivery; 90% of the bromelain group gained good scores compared with the rate of edema, inflammation and pain compared with 44%, which is in line with the results of this study (11).

Emmanuel and Aloy showed the effectiveness of combination of bromelain and trypsin (kotase®) on reducing postoperative pain on 5th and 10th days after laparotomy (14). Walker et al. showed that Bromelain reduces mild...
acute knee pain and improves well-being in a dose-de
dependent effect in a study of healthy adults (16). Kerkhoffs et al. found that bromelain and trypsin are effective on pain alleviation of acute lateral ankle sprain compared with placebo (17).

The REEDA in bromelain group was lower than placebo group. These results clearly demonstrated that bromelain has favorable effect on well repaired episiotomy wound healing. Emmanuel and Aloy showed the effectiveness of combination of bromelain and trypsin in reducing postoperative inflammatory edema (14); besides, Brown et al. in a double-arm crossover study reported that oral nutritional supplement containing bromelain, papain, trypsin and chymotrypsin accelerates soft tissue wound healing (7). Wound healing in 77% of patients was meaningfully less than the time when they used placebo, which is in line with our findings. However, the efficacy of each component of the supplement was not determined.

Contrary to this, Cowie et al. showed that bromelain (40 mg, four times a day) started from the day before surgery until six days after it, to patients undergoing elective plastic vaginal operations, had advantages for edema, hematoma and purulent discharge in days 5 and 14 after surgery, but did not reach a statistically significant level. The mean age of women was 49 - 59 years who were multiparous (12). It has been shown that along with increasing age, wound healing is delayed (18), which justifies the contradiction with the results of this study.

Considering the effects of bromelain on episiotomy wounds, Howat and Lewis stated that the rate of reduction of edema and bruising until the day 6 after labor in patients in bromelain group was faster compared to the placebo group. However, none of the results reached statistical significance, which could be simply due to inadequate dosing. Dosage of bromelain in this study was 40 mg, four times a day (13). Studies have shown that bromelain has a dose-dependent decrease of edema and inflammation.

The results of our study showed that the number of women who received bromelain was more compared with those who received placebo and that they achieved complete wound healing on 14th day after delivery; furthermore, they experienced no pain in this period. Similarly, in a study by Tassman, it was found that bromelain decreases bruise and inflation duration to 3.8 days, compared with 7 days in the placebo group. In addition, duration of pain was reduced to five days in bromelain group compared to 8 days in the placebo group (19).

Emanoel and Aloy showed that for those who received bromelain and trypsin, the average sedative usage was lower. Therefore, it can be effective for patients with contraindication (14). The findings of our study showed that, numerically, consumption of Acetaminophen in bromelain group was less compared with the placebo group, but did not reach a statistically significant level (Table 5). This could be due to small sample size.

### Table 5. Consumption of Acetaminophen in Bromelain and Placebo Groups

| Group       | Yes | No | P Value |
|-------------|-----|----|---------|
| Bromelain   | 14  | 27 | .07     |
| Placebo     | 22  | 19 | .07     |

a n = 41

#### 5.1. Trial Limitations
1. Complete control of psychological conditions of mothers and differences among people regarding this, was not possible.
2. Genetic and individual characteristics can influence wound healing, controlling them was not possible for the researcher.
3. It was not possible to fully control hygienic and nutritional conditions of mothers.
4. Pain is not a concrete issue and cannot be measured objectively. One has to measure it subjectively according to participants’ own sayings.

#### 5.2. Conclusions
The results showed the effectiveness of bromelain on episiotomy pain and wound healing. Therefore, we suggest using bromelain in postoperative period to speed up wound healing and reduce pain. Further double-blind controlled trial with a larger sample size is necessary to examine bromelain effects on reducing pain and wound healing using different dosing strategies.

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### References

1. Cunningham F, Bloom S, Hauth J, Gilstrap L, Wenstrom K. *Williams obstetrics.* 22 ed. New York: McGraw-Hill; 2005.
2. Suhrabi Z, Taghinejad H. A comparative study on the efficacy of ibuprofen and celecoxib on the intensity of perineal pain following episiotomy: a randomized clinical trial. *Iran Red Crescent Med J.* 2013;15(12):e9980. doi: 10.5812/ircmj.9980. [PubMed: 24693414]
3. Enkin M, Keirse M, Neilson J, Crowther C, Duley L, Hodnett E, et al. *Repair of perineal trauma.* Oxford,UK: Oxford university press; 2000.
4. Scott J, Gibbs R, Karlan B, AF AH, David N. Danforth’s obstetrics and gynecology. 9 ed. Philadelphia: Lippincott Williams and Wilkins; 2003.
5. Bin ED. Comparison of lavender and honey ointment on epis-
otomy pain and wound healing in primiparous women. Abvaz Fundishapur Uni Med Sci. 2007.
6. Karacem Z, Ergolu K. Effects of episiotomy on bonding and mothers’ health. J Adv Nurs. 2003;43(4):384–94. [PubMed: 12887357]
7. Brown SA, Coimbra M, Coberly DM, Chao JI, Rohrich RJ. Oral nutritional supplementation accelerates skin wound healing: a randomized, placebo-controlled, double-arm, crossover study. Plast Reconstr Surg. 2004;114(1):237–44. [PubMed: 15220599]
8. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. 2001;58(9):1214–45. [PubMed: 1577981]
9. Duskuova M, Wald M. Oral administration of proteases in aesthetic surgery. Aesthetic Plast Surg. 1999;23(1):41–4. [PubMed: 10022937]
10. Vellini M, Desideri D, Milanese A, Omini C, Daffonchio L, Hernandez A, et al. Possible involvement of eicosanoids in the pharmacological action of bromelain. Arzneimittelforschung. 1986;36(1):110–2. [PubMed: 3006709]
11. Zatuchni GI, Colombi DJ. Bromelain therapy for the prevention of episiotomy pain. Obstet Gynecol. 1967;29(2):275–8. [PubMed: 5334992]
12. Cowie DH, Fairweather DV, Newell DJ. A double-blind trial of bromelains as an adjunct to vaginal plastic repair operations. J Obstet Gynaecol Br Commonw. 1979;77(4):365–8. [PubMed: 4913414]
13. Howat RC, Lewis GD. The effect of bromelain therapy on episiotomy wounds—a double blind controlled clinical trial. J Obstet Gynaecol Br Commonw. 1972;79(10):951–3. [PubMed: 4563795]
14. Emmanuel RE, Aloy EA. A prospective randomized trial of Ko-tase® (Bromelain + Trypsin) in the management of post-operative abdominal wounds at the University of Nigeria Teaching Hospital Enugu, Nigeria. J College Med. 2005;30(2):56–6.
15. Davidson N. REEDA: evaluating postpartum healing. J Nurse Midwifery. 1974;19(2):6–8. [PubMed: 17338109]
16. Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults. Phytomedicine. 2002;9(3):381–6. doi: 10.1078/094471102321621269. [PubMed: 12587686]
17. Kerkhoffs GM, Struijs PA, de Wit C, Rahlfs VW, Zwipp H, van Dijk CN. A double blind, randomised, parallel group study on the efficacy and safety of treating acute lateral ankle sprain with oral hydrolytic enzymes. Br J Sports Med. 2002;36(4):431–5. doi: 10.1136/bjsm.2002.004150. [PubMed: 15273178]
18. Holt DR, Kirk SJ, Regan MC, Hurson M, Lindblad WJ, Barbul A. Effect of age on wound healing in healthy human beings. Surgery. 1992;112(2):293–7. [PubMed: 1647688]
19. Tassman GC, Zafar JN, Zayon GM. A Double-Blind Crossover Study of a Plant Proteolytic Enzyme in Oral Surgery. J Dent Med. 1965;20(5):1–4. [PubMed: 14282458]