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

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Received 2014 August 20; Revised 2014 September 23; Accepted 2014 November 1.

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 PGE 2 and Tromboxan B2 dose-dependently (8, 10). The fibrinolytic activity of bromelain has been attributed to enhanced conversion...
3.1. Intervention

Episiotomy pain was measured before the initial dose. 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 Groupsa

<table>
<thead>
<tr>
<th>Demographic Details and the Obstetric Information</th>
<th>Bromelain</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>23.97 ± 3.42</td>
<td>23.46 ± 3.82</td>
<td>.54</td>
</tr>
<tr>
<td>Body mass index before pregnancy</td>
<td>22.53 ± 1.61</td>
<td>22.90 ± 1.74</td>
<td>.96</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>39.3 ± 0.89</td>
<td>39.3 ± 1</td>
<td>.93</td>
</tr>
<tr>
<td>Cervical dilatation at intervention</td>
<td>2.8 ± 0.5</td>
<td>2.8 ± 0.8</td>
<td>.2</td>
</tr>
<tr>
<td>Length of rupture of membrane until delivery, min</td>
<td>411.88 ± 276.92</td>
<td>365.51 ± 279.75</td>
<td>.92</td>
</tr>
<tr>
<td>Length of labor stages, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>437.38 ± 198.32</td>
<td>426.17 ± 200</td>
<td>.67</td>
</tr>
<tr>
<td>Second</td>
<td>37.27 ± 30.25</td>
<td>33.64 ± 26.18</td>
<td>.44</td>
</tr>
<tr>
<td>Number of vaginal examinations during labor</td>
<td>8.59 ± 2.82</td>
<td>7.76 ± 2.62</td>
<td>.76</td>
</tr>
<tr>
<td>Length of episiotomy repair, min</td>
<td>14 ± 4</td>
<td>13.29 ± 3.79</td>
<td>.6</td>
</tr>
<tr>
<td>Number of skin sutures</td>
<td>5.51 ± 1.39</td>
<td>5.29 ± 1.15</td>
<td>.21</td>
</tr>
<tr>
<td>Newborn weight, g</td>
<td>3320 ± 367</td>
<td>3265 ± 324</td>
<td>.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Day</th>
<th>Study Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before initial dose (baseline)</td>
<td>Bromelain 5.9 ± 1.7</td>
<td>.74</td>
</tr>
<tr>
<td></td>
<td>Placebo 5.7 ± 1.4</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time (I)</th>
<th>Time (J)</th>
<th>Mean Difference (I-J)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>After ID</td>
<td>0.4634</td>
<td>.473</td>
</tr>
<tr>
<td>Baseline</td>
<td>Day 3</td>
<td>1.1463</td>
<td>.001</td>
</tr>
<tr>
<td>Baseline</td>
<td>Day 7</td>
<td>2.7683</td>
<td>.0001</td>
</tr>
<tr>
<td>Baseline</td>
<td>Day 14</td>
<td>5.0512</td>
<td>.0001</td>
</tr>
<tr>
<td>After ID</td>
<td>Day 3</td>
<td>0.683</td>
<td>.113</td>
</tr>
<tr>
<td>After ID</td>
<td>Day 7</td>
<td>2.3049</td>
<td>.0001</td>
</tr>
<tr>
<td>After ID</td>
<td>Day 14</td>
<td>4.5878</td>
<td>.0001</td>
</tr>
<tr>
<td>Day 3</td>
<td>Day 7</td>
<td>1.6220</td>
<td>.0001</td>
</tr>
<tr>
<td>Day 3</td>
<td>Day 14</td>
<td>3.9048</td>
<td>.0001</td>
</tr>
<tr>
<td>Day 7</td>
<td>Day 14</td>
<td>2.2829</td>
<td>.0001</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time (I)</th>
<th>Time (J)</th>
<th>Mean Difference (I-J)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 3</td>
<td>Day 7</td>
<td>1.646</td>
<td>.000</td>
</tr>
<tr>
<td>Day 3</td>
<td>Day 14</td>
<td>1.9146</td>
<td>.000</td>
</tr>
<tr>
<td>Day 7</td>
<td>Day 14</td>
<td>1.2683</td>
<td>.000</td>
</tr>
</tbody>
</table>

The mean difference is significant at the 0.05 level.

5. Discussion

In this trial, reduction in VAS was more in bromelain group compared to the placebo group. Zatuchni and Colombo 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-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, 4 times a day for 6 days (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 infiltration 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>
<thead>
<tr>
<th>Group</th>
<th>Yes</th>
<th>No</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bromelain</td>
<td>14</td>
<td>27</td>
<td>.07</td>
</tr>
<tr>
<td>Placebo</td>
<td>22</td>
<td>19</td>
<td>.07</td>
</tr>
</tbody>
</table>

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.

Acknowledgments
I would like to thank the research center of Jondishapur university of medical sciences of Ahvaz for supporting this project. In addition, we are grateful to manager of Amiralmomenin hospital as well as delivery, postpartum and gynecology clinic staff for their assistance.

Footnote
Funding/Support: Ahvaz Jundishapur university of medical sciences supported this study financially.

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