

Investigating the effect of edible pineapple on the ripening of the cervix and the onset of labor.

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Abstract

Background

Labor induction in post-term pregnancies is still one of the most common midwifery interventions, and preparation of the cervix before labor induction is one of the most important reasons for the success of labor. Therefore, this research was conducted to investigate the effect of edible pineapple on ripening the cervix and the onset of labor.

Methods

In this randomized controlled clinical trial, 66 pregnant women with a gestational age of 40–41 weeks, referring to the maternity of Omo Albanin Hospital in Mashhad, were selected and randomly divided into two intervention and control groups, and the Bishop Cervix score at the time of study entry. It is registered. Women in the intervention group consumed a 250-gram packet of edible pineapple every 24 hours for 3 consecutive days. In the control group, routine care was performed. Research units were followed up in terms of Bishop's Cervix score and labor onset symptoms 48 and 72 hours later and during hospitalization. Data collection tools were personal and midwifery information questionnaires, observation and examination forms, daily records, and follow-ups, which were used for content validity and simultaneous observation to check the tool's reliability. The data was analyzed using SPSS 18 repeated measures comparison test. A significance level of 0.05 was considered.

Results

According to T-test, two groups were homogeneous in terms of age ($p = 0.439$). The average Bishop score was the same at the beginning of the study and according to the analysis of variance test with repeated values, the changes in the first 48 hours, 72 hours after the start of the study, and hospitalization time were significantly different between the two groups ($p < 0.001$). There was a significant difference ($p < 0.001$) in the time of labor and the amount of oxytocin used in the intervention and control groups. The two intervention and control groups had no significant differences between the Apgar scores of the first and fifth minutes of the newborns, the contamination of the amniotic fluid with meconium, the type of delivery, and the condition of the fetal heart during hospitalization.

Conclusion

Daily consumption of edible pineapple positively affects the progress of labor to prepare the cervix and induce labor and does not harm the mother and the fetus. It is also suggested to use a larger sample size and time to start consumption at a gestational age of fewer than 40 weeks and a longer duration of pineapple consumption in future research.

Background

Childbirth is a part of the natural physiological process and it happens spontaneously when the pregnancy period is completed without complications, and at this time, the cervix is often ready for childbirth (1, 2). Also, natural childbirth requires many changes and transformations in the function of the uterus and cervix. Before contractions begin, the cervix must undergo extensive deformation. Changing the shape of the cervix includes changes in the soft tissue, which is called ripening of the cervix, and is one of the main steps at the beginning of labor (3). Preparation of the cervix before induction of labor is necessary for the success of labor and is one of the most common measures in the termination of pregnancy (4, 5).

The researchers of "Safe Labor Consortium" state that elective induction has resulted in vaginal delivery in 97% of multiparous women and 76% of nulliparous women, but induction of labor has been more successful if the cervix is ready, and the possibility of cesarean delivery is related to Induction is strongly influenced by the time spent for induction (especially in cases of the unfavorable cervix) (3).

Women undergoing elective induction undergo more interventions such as amniotomy, electronic fetal monitoring, and epidural anesthesia compared to women who have spontaneous labor (6). Also, cesarean delivery, Chorioamnionitis, uterine scar rupture, and postpartum hemorrhage due to uterine atony, uterine tachysystole, and fetal heart rate changes are maternal and fetal complications related to Liberia induction (3). For this reason, there is an effort to prepare the cervix by various methods before induction of labor (7).

Various medical methods for preparing the cervix include prostaglandin E1 and E2 (in the form of gels, suppositories, and oral tablets) and mechanical methods including (intracervical Foley catheter with or without extra amniotic injection of normal saline, cervical hygroscopic dilators) and tearing of the curtains (3) and other methods include nipple stimulation, acupuncture, sexual intercourse, enema and medicinal plants (8). Medical and surgical methods have significant side effects such as bleeding during and after delivery, prolonged delivery, suffering and fetal injuries and uterine rupture(9), and tearing of the membranes with pain, vaginal bleeding, and irregular contractions without accompanying labor(3). Therefore, finding a method that helps prepare the cervix with fewer complications has always been of interest.

Among these solutions is the use of medicinal plants that are usually used to prepare the cervix, including castor oil (10, 11), red raspberry leaf (12), primrose oil (13), sodas and (9) and evening primrose oil (14) and dates (15–17). Pineapple is one of the fruits mentioned in various cultures to start childbirth. Pineapple is a plant from the bromelainase family and is one of the foods that stimulate labor (2). Pineapple (*Ananas Comosus*) contains phytonutrients, vitamin C, and a compound called bromelain. Bromelain is a proteolytic or protease enzyme that is found only in the pineapple plant and its highest amount is in the stem and fruit of pineapple (18). Most of the medicinal effects of bromelain are related to its proteolytic properties (19) and it has various therapeutic properties such as anti-asthma, anti-inflammatory, fibrinolytic, anti-cancer, antibiotic, anti-thrombotic and anticoagulant (18).

In the traditions of old medicine, pineapple is known to induce abortion in pregnant women and as a pain reliever, and in other words, because it has a contraction effect on the muscles of the uterus, it can be used in prolonged pregnancy to prevent medical interventions (20). In the study of Faezeh Manji et al. (2016) at the Gynecology and Obstetrics Center of Singapore, the effect of pineapple extract on the contractile activity of rat and human uterine myometrium samples was shown (20), and in another study by Nwankudu et al (2015) the oxytocin effect of pineapple juice on muscle contractions. The uterus of mice has been investigated and confirmed (21). It is also stated in the study of Padma (2012) that pineapple bromelain enzyme is effective in uterine contractions by stimulating prostaglandin secretion (22).

Oral bromelain dose-dependently decreases plasma bradykinin and prostaglandin E2 levels and increases prostacyclin in inflammatory areas (23). Considering that prostaglandin E2 keeps the uterus relaxed (3), reducing the level of prostaglandin PGE2 can cause uterine contractions. Also, an increase in prostacyclin causes an increase in collagenase enzyme and muscle relaxation. The effect of bromelain plant protease by inhibiting the effect of collagen in the process of angiogenesis has also been observed in the laboratory study of Mushtaq et al(2019) (24). So, with the process of preparation of the cervix, which includes the change in the shape of the connective tissue, the decrease in the concentration of collagen and proteoglycan, and the increase in water content compared to the non-pregnant uterus (3), it can cause the preparation of the cervix for childbirth.

Although no research shows the effect of bromelain on the initiation of uterine contractions in humans, in many cases it is generally recommended for pregnant women to initiate labor, and some researchers also believe that the fiber and sugar in pineapple are due to intestinal-digestive movements. It affects creating freedom (2). It may be possible to justify the effectiveness of pineapple on the cervix with the following mechanisms:

Firstly, the main factor in the structural arrangement of the cervix is collagen (3) and on the other hand, bromelain enzyme increases the hydrolytic activity in the connective tissue, especially on collagen (18). It has been mentioned that the hydrolysis of collagen by bromelain increases the elasticity and flexibility of the uterine muscle (18). And since collagen is responsible for the main arrangement of the connective tissue of the cervix, this effect can also justify the effectiveness of pineapple in the preparation of the cervix. Secondly, the bromelain enzyme is an external proteolytic enzyme in the cysteine proteinase group, which is widely used for the regression of connective tissue (25), which may be one of the reasons for the effect of bromelain enzyme on cervical connective tissue to soften and prepare the cervix, its proteolytic effect. Thirdly, the significant changes that occur in the extracellular matrix during the ripening of the cervix in the second stage of pregnancy are associated with the invasion of inflammatory cells into the stroma. In this model, the chemical absorbents present in the cervix attract inflammatory cells to the site, and these cells also release proteases that may facilitate the breakdown of collagen and other matrix components (3). Also, by stimulating leukocytes, bromelain increases the level of interleukin 6, 1, 8 and tumor necrosis factor-alpha in the inflamed area. The increase of cytokines, especially interleukin 8, leads to the recruitment of granulocytes and monocytes to the inflammatory area and increases the activity of

phagocytosis and chemotaxis (19). Therefore, according to the above mechanisms, probably pineapple with bromelain enzyme can prepare the cervix

Therefore, considering that the goal of midwifery is to emphasize natural and safe childbirth by maintaining the health of the mother and fetus and using non-pharmacological approaches, performing vaginal delivery without medical intervention (induction of labor), and preventing prolonged labor for the mother and the fetus is vitally important (9). Therefore, the current study was designed and implemented to determine the effect of pineapple consumption on the readiness of the cervix and the onset of labor.

Method

In this randomized controlled clinical trial study, 64 pregnant mothers with a gestational age of 40–41 weeks were referred to the maternity ward of Omo Albanin Hospital in Mashhad. The subjects were selected by the access method and were divided into two groups (intervention, control) by simple random assignment method. Due to the lack of a completely similar study, the sample size was determined based on the effect size formula and considering the error of 5% and the test power of 80%, and the average effect size (0.5) of 30 people in each group.

The researcher presented an official letter of introduction from the Mashhad Nursing and Midwifery College and went to Omo Albanin Hospital in Mashhad City after obtaining approval from the relevant authorities, she settled in the hospital to collect information and take samples. The criteria for mothers to enter the study include maternal age of 18–35 years, gestational age of 40–41 weeks based on the first day of the last menstrual period or ultrasound under the first trimester of pregnancy, singleton fetus with the cephalic presentation, presence of normal AFI according to the ultrasound of the third trimester of pregnancy, absence Allergy to pineapple, no known chronic disease, no history of cesarean section or childbirth complications (hydramnios, oligohydramnios, preeclampsia, eclampsia), Bishop's score less than or equal to 4, healthy amnion sac, normal non-stress test, no sexual intercourse from 24 hours before From the beginning of the study to the end of it, no use of any herbal medicine three days before and during the study.

Informed consent

was signed by each patient regarding the intervention application, its possible complications, and outcomes. This study protocol was approved by the Medical ethics committee of Mashhad University of Medical Sciences with the ethical code IR.MUMS.NURSE.REC.1397.055 and all methods in this study were carried out in accordance with relevant guidelines and regulations of RCT studies.

At the beginning of the study, the researcher identified the research units in three shifts, morning, evening, or night, among the mothers who went to the midwifery clinic of the hospital without labor symptoms to determine the time of delivery or pregnancy control, or with a complaint of passing the due date of delivery, and after describing The purpose and method of the research was included in the study after obtaining written consent (pregnancy age was calculated according to LMP or based on ultrasound of

the first trimester). The selection form of the research unit was completed through study, interview, taking a complete history, and viewing ultrasounds and pregnancy control records. First, a preliminary examination was performed to determine the Bishop score of the cervix, and the research units were included in the intervention if they had a Bishop score of less than or equal to 4. An equal number of "a" and "b" cards were placed in a box, and the mothers were assigned to one of the study groups by removing the "a" (intervention) and b (control) cards.

To avoid storing more than 72 hours divided and packaged pineapples, fresh pineapples were purchased from the fruit shop immediately after the selection of the research unit. Then its skin was separated and three 250g packs for each mother were packed in disposable containers and delivered to the research unit. The mother was advised to keep the fruit on the middle shelf of the refrigerator and to consume a whole pack every 24 hours alternately or all at once according to her wish (for 3 consecutive days). In addition, both intervention and control groups received routine measures. Both groups were asked to return to the maternity hospital 48 and 72 hours after the start of the intervention in case of no onset of labor symptoms, so that a vaginal examination can be performed to determine the Bishop's score, as well as auscultation of the fetal heart and, if necessary, an echocardiogram of the fetus.

The time of the onset of labor was investigated in three time periods within 48 and 72 hours from the start of the intervention and the hospitalization time of the mothers.

It should be noted that the examinations of the subjects in subsequent visits were performed by the assistant researcher, who was unaware of the type of groups. During the study, the research units were asked to contact the maternity hospital in case of labor pains, spotting or bleeding, discharge, reduced fetal movements, or any other problem while calling the researcher. With the onset of labor symptoms and hospitalization of the patient (Bishop Cervix score was also determined at the time of hospitalization), her follow-up was done by the researcher and assistant researcher from the time of hospitalization until the end of delivery. Demographic and midwifery information questionnaires and research unit follow-up form and research unit information from the beginning of hospitalization to delivery, which includes the date and time of hospitalization, the reason for visiting the maternity hospital, initial examinations at the time of admission (vital signs, fetal heart rate, and vaginal examination) Childbirth, use of cervical preparation methods and its type, use of oxytocin, type of delivery, newborn's Apgar score, degree of amniotic fluid contamination with meconium were recorded by the researcher and the researcher's assistant using records and observation. Also, the daily registration form for fetal movements (with training) was given to the mother to be completed by the research unit during the intervention, and the fetal heart rate was taken from the mothers every other day until hospitalization. Finally, the average cervical preparation score in the two groups was determined and compared during the three time periods mentioned. Also, the time of the onset of labor was recorded and compared in both groups (during the first 48–72 hours and hospitalization time) from the beginning of the intervention. The economic status of the family according to the family income was divided into 3 levels (below the sufficiency level, above the sufficiency level, and more than the sufficiency level), and the level of education was also considered into 5 levels (illiterate, elementary, secondary, diploma and university).

After collecting and recording data in SPSS software version 18, the data were analyzed in two descriptive and analytical formats by a statistician who was unaware of the division of the intervention and control groups at a significance level of $\alpha = 0.05$. In the analysis section, the normality of data distribution was checked and t-test, chi-square, and repeated measures analysis of variance were used to answer the hypotheses of this study.

Results

In this study, 66 pregnant women were examined, 36 in the intervention group and 30 in the control group. In the control group, we had 6 people dropped out of the study. 2 people were excluded from the study due to the mother's visit to the doctor's office and vaginal examination and the possibility of cervical stripping, 3 people were excluded from the study because they did not visit and 1 person was excluded from the study because of having sex. The average age of the intervention and control groups was 26.4 ± 4.47 and 27.3 ± 4.41 respectively. There was no statistically significant difference between the ages of the two groups (p -value = 0.439). The majority of the participants had primary education (18 people (27.3 percent)) and were housewives (48 people (72.7 percent)). The demographic information of the participants according to the treatment groups is presented in (Table No. 1). The two groups were similar in terms of age, education level, occupation of the woman and her husband, and economic status of the family.

The mean gestational age and birth weight of the baby were not significantly different between the two groups. Also, in terms of the type of pregnancy and the number of pregnancies, the heart rate of the fetus at the time of admission, no significant difference was observed between the two study groups (Table No. 2).

In the intervention group, more cervical dilatation and amnion sac rupture were observed than in the control group. But more blood secretions were recorded in the control group. There was a significant difference between the two study groups in terms of labor onset symptoms. In the pineapple consumer group, only 3 people (8.3 percent) used cervical preparation methods, while in the control group, 23 people (76.7 percent) used these methods, and the two groups had a significant difference in They used the methods of preparing the cervix. In mothers consuming pineapple, oxytocin was used for 6 people (16.7%) during labor, while in the control group, oxytocin was used for 17 people (56.7%) for strengthening. Contractions were used ($P = 0.001$). (Table No. 3)

The mean score of Bishop's score before the intervention was not significantly different between the two groups (p -value = 0.566), but over time, changes in addition were observed between the Bishop scores of the two groups. To compare the changes in the Bishop score in the two study groups, the repeated measures test was used with the control of baseline values. Based on the obtained results, in addition to the increase in Bishop's score over time, significant changes in Bishop's score were seen as a result of the intervention used (p -value < 0.001). That is, the consumption of pineapple has caused a greater increase in Bishop's score. (Table No. 4 and Fig. 1)

Finally, we compared the consequences and possible complications of childbirth of participants between study groups. As the results show only induction duration was statistically significant between control and intervention groups. (Table No. 5)

Discussion

Outpatient use of herbal and oral medicines as one of the non-pharmacological solutions with fewer side effects to prepare the cervix and induce labor has always been the focus of researchers. As some examples, Razali et al. (2017), Kariman (2015), and Kordi (2013) investigated the effect of dates on the onset of labor (26). Okoro et al. (2019), Gilad (2018), Kohnmoi Aghdam (2014), and Sabri (2008) investigated the effect of edible castor oil on the onset of labor (11). Kelati et al. (2018) investigated the effect of evening primrose oral capsule on cervical readiness, and Najafi (2019) and Hashminejad (2019) also investigated the effect of vaginal evening primrose on cervical readiness and labor initiation (26).

Pineapple is one of the fruits mentioned in various cultures to start childbirth. In the study of Faze Manji et al. (2016), pineapple extract caused contractile activity in mouse and human uterine myometrium samples (20), and in the study of Nwankudz (2015), ripe pineapple fruit juice caused contraction of the uterine muscles of non-pregnant mice (21). Pineapple bromelain enzyme is effective in uterine contractions by stimulating prostaglandin secretion (13). Prostaglandin also improves the preparation of the cervix by increasing the water under the cervical mucosa and causing changes in the collagen bands and causing an increase in the sensitivity of the uterine myometrium to oxytocin (3). In the study of Harianja (2017), which examined the effect of pineapple juice on the fundal height of primiparous mothers in the postpartum period, in addition to the effect of bromelain in stimulating prostaglandin secretion and its contractile effect on the uterine myometrium, the proteolytic property of pineapple bromelain enzyme on connective tissue and collagen Uterine myometrium is effective in uterine involution (18).

Considering the effects of pineapple in the above articles and the review of various articles, no study was found that investigated the effect of pineapple consumption on the onset of labor in human samples. This study was conducted to investigate the effect of pineapple consumption on the preparation of the cervix and the onset of labor in primiparous women.

The findings of the research showed that in the pineapple-consuming group, 63.9% of the mothers had labor symptoms within 72 hours after the intervention, while in the intervention group, most of the mothers had these symptoms at the time of hospitalization and more than 3 days had passed. In the pineapple-consuming group, only 8.4% of cases used one of the methods of preparing the cervix, including extra-amnion tube and misoprostol, while in the control group, 76.7% of the mothers used one of these two methods, which indicates that Better Bishop's score and better preparation of the cervix in the intervention group. Also, the percentage of oxytocin use and the duration of oxytocin use to strengthen labor contractions in the control group were significantly higher than the intervention group ($P = 0.001$) and ($P < 0.001$).

Pineapple bromelain enzyme is effective in uterine contractions by stimulating prostaglandin secretion (22), which is comparable to the present study due to the similar mechanism of the date effect, which can act on prostaglandin receptors and cause early stimulation of uterine contractions (27). In the study of Kurdi (16) and Kariman (17) entitled "Effect of Dates on the Beginning of Labor", a significant increase in the spontaneous onset of labor was reported, which was in line with the present study. In the present study, 63.9% of mothers were hospitalized with cervical dilatation, which is one of the signs of labor. However, in Razali et al.'s study (2017), dates did not affect the spontaneous onset of labor (15), which was not consistent with the results of our study. Razali's study started with a larger sample size and only in primiparous mothers with a gestational age of 36 weeks, which can be one of the reasons for not being consistent with the present study. According to the results of some studies, which show that castor oil Ricinoleic acid increases the readiness of the cervix and uterine contractions with the effect of EP3 prostaglandin receptors on the uterine and intestinal smooth muscles (26), the results of the relevant studies are comparable with the present study. In Pirdade Biranvand's (28) and Azarkish's (29) study titled the effect of oral castor oil on the Onset of Labor, a significant increase in the spontaneous onset of labor symptoms was reported, which was consistent with the present study. In Saberi's study (30), with the effect of castor oil on labor induction, only the onset of labor was considered, which was in line with the present study. However, in the old study of Aghdam (31), castor oil did not have a significant effect on the onset of labor, and in the study of Gilad (32), castor oil did not have a significant effect on the spontaneous onset of labor in primiparous mothers, and it is not consistent with the present study, which could be due to the sample size. Higher in these two studies and the possibility of using a placebo and reducing the possibility of bias compared to similar studies and the present study.

According to the findings of the present study, the average score of Bishop in the pineapple group compared to the control group increased significantly within 48 hours from the start of the intervention ($p = 0.001$) and 72 hours after the start of the intervention ($p < 0.001$), as well as the average score Bishop at the time of hospitalization, was 8.08 in the intervention group and 4.30 in the control group, which had a significant difference ($p < 0.001$). In the study of Kurdi and Kariman, a significant increase in Bishop's score was reported, which was consistent with the present study. Bishop's score was not evaluated in Razali's intervention. A significant increase in Bishop's scores was also reported in the study of Pirdade Biranvand(28) and Azarkish(29), which was in line with the present study. In Saberi's study (30) with the effect of castor oil on induction of labor, Bishop Cervix scores were not considered. In the ancient study of Aghdam (31), castor oil did not have a significant effect on Bishop's score.

In Najafi's study (33), the effect of taking evening primrose capsules from week 38 to delivery was investigated, which was effective on Bishop's score and was consistent with the present study. Evening primrose contains large amounts of essential unsaturated fatty acids that facilitate the synthesis of prostaglandins. He does. Prostaglandins play an essential role in the preparation process of the cervix by affecting pro-inflammatory factors such as cytokines and leukocytes (27). Therefore, considering the similar mechanism mentioned in the effect of pineapple on the preparation of the cervix, it is comparable. In Hasheminejad's study (34), despite taking twice the dose of vaginal evening primrose capsules compared to Najafi's study, evening primrose was not effective on the onset of labor, which is not

consistent with our study, and the reason for this could be the use of capsules in the 37th week of pregnancy and only by mothers. be a virgin However, the present study was conducted in primiparous mothers of 40 weeks and more, which can be justified due to the greater increase in oxytocin receptors and greater preparation of the cervix with increasing gestational age, in addition to this, elective induction before the 39th week of pregnancy has a significant amount of adverse and severe side effects. The period of infancy will be accompanied (3).

In the study of Harianja (2017) entitled "Investigation of the effect of pineapple juice on the height of the uterus after delivery", pineapple has been effective in increasing the contraction of the uterus and the return of the uterus in the postpartum period due to the presence of bromelain enzyme and its effect on the collagen level and with its hydrolytic properties. 18). Although the results of this study are not the same as the purpose of the present study, they are in line with the study done in justifying the effect of pineapple on uterine contractions and helping to start labor as a result of uterine contractions. In the Haryana study, 250 grams of pineapple juice containing fruit puree was given to the research units daily for 7 days. While the mothers in the present study were pregnant and the time of the intervention started from the 40th week of pregnancy and the probability of the mothers being hospitalized at 41 weeks due to various reasons by the doctors or the insistence of the mothers was high, consuming 250 grams of pineapple for 3 days It was recommended.

In the present study, there were no significant differences between the two groups in amniotic fluid color, Apgar scores of 1 and 5 minutes, and type of delivery. In this study, mothers' willingness to consume pineapple fruit was very high, which is considered one of the strengths of the study. Due to the pleasant taste of pineapple, the researcher did not face any problems in consuming the fruit. In addition, due to the possibility of using it at home, it is possible to avoid the problems related to visiting medical centers and related costs that are seen in other methods such as acupuncture or acupressure.

Among the limitations of this study, the following points can be mentioned: the accuracy of the research units in consuming the specified amounts of fruit completely by the individual himself, the inability to blind the patients as the main blinding part of the clinical trial studies, the physical characteristics of the subjects in the labor process. And childbirth, psychological characteristics, and personality characteristics of people in learning the training provided were effective in how to answer the questions of the questionnaire, which were not fully controllable, and the researcher made the accuracy of the statements of the research units a criterion. Also, another limitation was the high price of pineapple fruit in Iran, which in addition to the high cost of the study, it may be difficult to obtain this fruit for poor socio-economic classes.

Conclusion

Based on the findings of this research, it seems that the consumption of pineapple fruit orally is effective in the preparation of the cervix and the beginning of labor in pregnant mothers, and the consumption of this fruit can be recommended at the end of pregnancy. The amount of fruit consumed was considered to

be within the range of safe doses for the mother and fetus and can be consumed daily in this study. Finally, according to the positive effects of using vaginal methods in labor induction and the positive effect of pineapple bromelain in cervical preparation, research entitled Investigating the effect of vaginal bromelain in the onset of labor and cervical preparation with more samples is suggested.

Abbreviations

RCT

Randomized controlled trial

Declarations

Ethics approval and consent to participate

The study was approved by The Medical ethics committee of Mashhad University of Medical Sciences. Ethical Lot Number: IR.MUMS.NURSE.REC.1397.055 and registered in the clinical trial database of Iran with the code IRCT20181007041266N2 the hold on (15/01/ 2019). We confirm that all methods were carried out in accordance with relevant guidelines and regulations.

For participants who are illiterate, we provided informed consent from their legal guardian/ a legally authorized representative. It is not applicable under Consent for publication our study.

Consent for publication

It is not applicable.

Availability of data and materials

It is available. All relevant data are within the paper and its Supporting Information files.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors read and approved the final manuscript. **SSM** participated in the conception and design of the study, coordinated the study, collected data, participated in the data analysis and interpretation of data, and wrote the manuscript. **RM** participated in data collection, conducted the data analysis, assisted with

the interpretation of the data, and commented on the manuscript. **MR** participated in the data collection, the interpretation of data, and co-wrote the manuscript. **ES & RM** participated in the conception and design of the study, assisted in the interpretation of the data, and commented on the different versions of the manuscript. **YR & SSM** participated in the conception and design of the study, data collection, the interpretation of data, and co-wrote the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 to 5 are available in the Supplementary Files section.

Figures

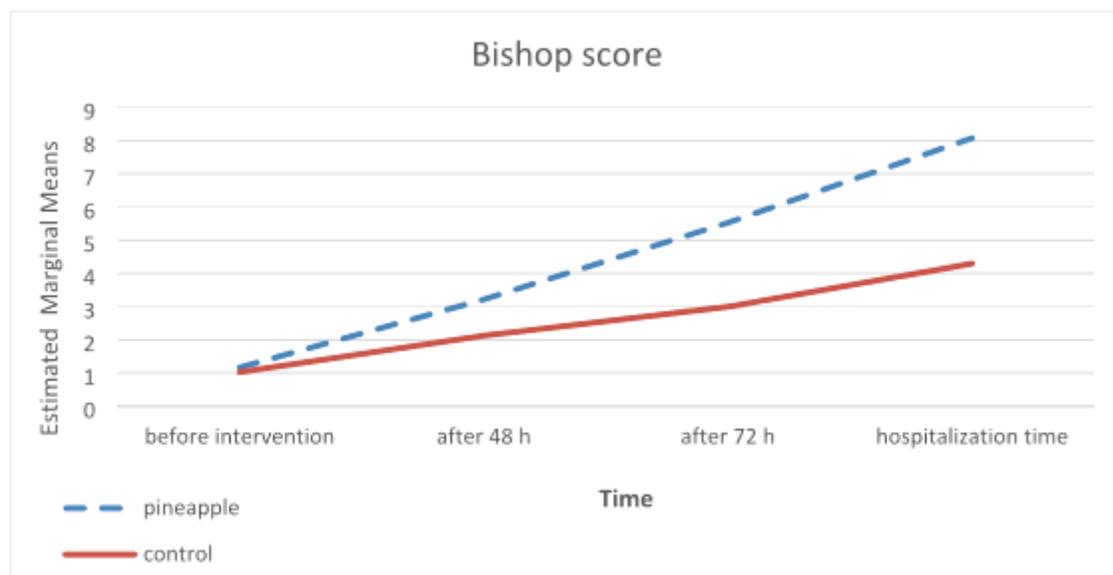


Figure 1

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