Journal of Midwifery & Women's Health www.jmwh.org

Original Research

Use of Hyaluronidase to Prevent Perineal Trauma During Spontaneous Births: A Randomized, Placebo-Controlled, Double-blind, Clinical Trial

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Introduction: The purpose of this study was to compare the frequency and severity of perineal trauma during spontaneous birth with or without perineal injections of hyaluronidase (HAase).

Methods: A randomized, placebo-controlled, double-blind clinical trial was conducted in a midwife-led, in-hospital birth center in São Paulo, Brazil. Primiparous women (N = 160) were randomly assigned to an experimental (n = 80) or control (n = 80) group. During the second stage of labor, women in the experimental group received an injection of 20.000 turbidity-reducing units of HAase in the posterior region of the perineum, and those in the control group received a placebo injection. The assessment of perineal outcome was performed by 2 independent nurse-midwives. A 1-tailed Fisher exact test was performed, and a P value $< .025$ was considered statistically significant.

Results: Perineal integrity occurred in 34.2% of the experimental group and in 32.5% of the control group, which was not a statistically significant difference ($P = .477$). First-degree laceration was the most common trauma in the posterior region of the perineum in women in both groups (experimental = 56%, control = 42.6%). Severe perineal trauma occurred in 28.9% of the experimental group and 38.8% of the control group, which also was not a statistically significant difference ($P = .131$). The depth of second-degree perineal lacerations in the experimental and control groups, measured by the Peri-Rule, was 1.9 cm and 2.3 cm, respectively. An episiotomy was performed in 11 women (experimental group = 3, control group = 8), and 4 (all in control group) had third-degree lacerations.

Discussion: The use of injectable HAase did not increase the proportion of intact perineum and did not reduce the proportion of severe perineal trauma in our sample.

J Midwifery Womens Health 2011;56:436–445

Keywords: intrapartum care, second-stage labor, normal birth, hyaluronidase, perineal trauma

INTRODUCTION

The prevalence of perineal trauma during birth varies in different settings, depending on the practices adopted at birth as well as the maternal and fetal conditions. Parity, maternal age, presentation, and fetal weight are well-known antepartum factors that affect the frequency and severity of perineal trauma.[1–4] Intrapartum factors that affect perineal trauma include oxytocin augmentation, epidural anesthesia, lithotomy position, bearing down efforts, and the practices of the professional who is attending the birth. Some maneuvers, techniques, and materials have been promoted as protective for the perineum in childbirth.[4–7] One of these is hyaluronidase (HAase).

Biochemistry and Biological Properties of Hyaluronidase

Hyaluronidase is an enzyme complex present in several human organs and tissues. The enzyme acts on hyaluronic acid (HA), which is a viscous mucopolysaccharide present in loose connective tissue. Hyaluronic acid is an important component of the extracellular matrix and is responsible for keeping cells attached to each other, providing support and anchorage for cells, segregating tissues from one another, and regulating intercellular communication. Hyaluronidase has the ability to depolymerize and hydrolyze HA, reducing its viscosity and increasing the permeability of cell membranes and blood vessels. This enzyme alters the structure and the physical and chemical characteristics of the tissue without breaching the blood-brain barrier in healthy persons.[8]

Although there is a lack of clinical evidence, the biological plausibility to support the effectiveness of HAase to prevent perineal trauma is due to its property of influencing the physical and chemical characteristics of loose connective tissue without crossing the blood-brain barrier in healthy individuals. In turn, the loose connective tissue is part of the genital tract and perineal structure constitution, both displaying the same basic structural organization, with a smooth muscle wall, an internally located mucosa, and an outer layer of loose connective tissue.

Hyaluronidase is rapidly eliminated from plasma (early stage), then begins an intermediate phase of elimination with the passage of enzyme from the intravascular environment to the extravascular environment. In the final phase, the enzyme is inactivated and eliminated. The HAase enzymatic effect in tissues lasts at least 12 hours. After 2 to 4 days, the previous structure of the tissue is restored. Regarding HAase toxicity, no pathological changes were detected in human organs, and no mutagenic effect has been found in previous in vitro and in vivo research conducted on the use of HAase.[8,9]

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 1526-9523/09/$36.00 doi:10.1111/j.1542-2011.2011.00056.x

In laboratories, the HAase is synthesized from bovine testicles. The preparation for therapeutic use is highly purified and is lyophilized, sterile, pyrogen-free, colorless or slightly yellow, and odorless.[8]

The Use of Hyaluronidase in Childbirth

Between 1950 and 1960, the first reports were published regarding the use of HAase to reduce the number of perineal lacerations and the need for episiotomy during childbirth. The number of studies is small, but most of them suggest that when this enzyme is injected into the perineum during the second stage of labor, more women have an intact perineum and fewer have an episiotomy.[10–18]

Nevertheless, 2 randomized controlled trials (RCTs) reported diverging results.[17,18] In the first, with the injection of HAase in 100 women during birth, there was a reduction in episiotomy, and perineal integrity was 3 times more frequent in the group of women who received the HAase injection. In the second RCT, conducted with 200 primigravida patients divided into 3 groups (HAase, saline solution, and no injection), the researchers found no statistically significant difference in the rates of episiotomy, spontaneous lacerations, or intact perineum. In both studies, there were no adverse outcomes when women were followed between 4 and 6 days and 6 weeks after birth. All previous studies cannot be compared because of differences in methodology and doses.

Most recently, a third RCT conducted between 2002 and 2003 with 139 primiparous women showed that injection of HAase increased perineal integrity more than twice when compared with the group that did not receive HAase injections, and there were no cases of second-degree or higher lacerations.[19] However, the authors indicated the need for further research to better assess the effectiveness of HAase for the prevention of perineal trauma during spontaneous births. That study was the main reference for the present research and was adopted as the pilot for the research reported here. The 3 RCTs are summarized in Table 1.[19]

Considering the favorable outcomes and recommendations of the pilot study,[19] the purpose of the present research was to compare the frequency and severity of perineal trauma during spontaneous births with or without perineal injections of HAase. A randomized, placebo-controlled, double-blind trial was conducted to test the hypothesis that the injection of HAase into the perineum during the second stage of labor 1) increased the proportion of perineal integrity and 2) reduced the proportion of severe perineal trauma.

The study was conducted at the Amparo Maternal Birth Centre in São Paulo, Brazil. This center is a midwife-led, in-hospital birth center for women with low to medium–risk pregnancies. An average of 900 births per month occur in the birth center, and midwives or nurse-midwives attend all spontaneous births. A team of obstetricians admits women in labor, performs cesarean births, and intervenes in cases of dystocia. Episiotomies are avoided and performed only on a restrictive basis according to standard protocols. Conditions requiring episiotomies include fetal distress, large fetus, slow fetal expulsion, and imminent risk of third-degree laceration. All women have a companion of choice and nonmedical support from a doula during childbirth.

METHODS

The study protocol was registered in the Latin American Clinical Trials Register (www.latinrec.org. Number BRA88), was approved by the research and ethics committee of the School of Nursing of Universidade de São Paulo, and was authorized by the clinical board of the birth center. Women were admitted to this study during labor after receiving oral and written information from the researchers and after giving voluntary consent. The study outline was reviewed with participants before they signed the consent forms.

Participants (N = 160) were randomly assigned to 1 of 2 groups during the second stage of labor by using a computerized, random-numbers table previously generated by the statistician. Groups consisted of the experimental group (n = 80, treated with HAase injection) and the control group (n = 80, treated with placebo injection). Inclusion criteria were: age 18 years or older; no prior record of vaginal birth; term, single, and live fetus; vertex fetal presentation; cervical dilation at least 8 cm on admission to the birth center; no suspected or confirmed systemic infections or infections of the perineal or vulvovaginal region; and spontaneous birth in a semisitting position without intradural or extradural anesthesia.

The primary outcomes were perineal integrity (absence of episiotomy or any laceration in the posterior region of the perineum) and severe perineal trauma (higher than first-degree laceration or episiotomy). As reported in the introduction, episiotomies categorized as second-degree, third-degree, and fourth-degree lacerations were grouped together because of the hypothesis that a supple perineum accomplished by the HAase injection may avoid each of these types of perineal trauma.

The independent variable was the use of HAase during the second stage of labor, and dependent variables were the perineal outcomes, considering the following definitions[20]: 1) Perineal integrity: absence of episiotomy or any laceration in the posterior region of the perineum; 2) First-degree laceration: involves the fourchette, perineal skin, subcutaneous tissue, and vaginal mucous membrane; 3) Second-degree laceration: involves superficial muscles (bulbocavernosus and transverse), and when it is deep, the pubococcygeus muscle is also affected; 4) Third-degree laceration: involves the sphincter anal complex (3a, less than 50% of external anal sphincter; 3b, more than 50% of the external anal sphincter; 3c, internal anal sphincter torn); 5) Fourth-degree laceration: involves the sphincter anal complex and anal epithelium; and 6) Episiotomy.

The other variables considered were: maternal and neonatal characteristics (age, race/color, education level, conjugal status, birth weight, Apgar scores), bearing down efforts, depth and length of perineal lacerations, and postpartum perineal conditions. The measurement of lacerations was done using the Peri-Rule, which is a soft, plastic device with a millimeter scale printed on. This tool was sterilized with ethylene oxide and was single-use only.

The strategy for calculating the sample size was based on calculation of sample size for comparing 2 proportions.[21] The sample was defined in order to satisfy the condition chosen by the researchers and was based on data obtained from the pilot study.[19] In the pilot study, 32% of the control group had perineal integrity, and there was a 14% difference in second-degree lacerations between the intervention and control groups. Thus, the difference considered clinically important to be detected was an increase of 25% in perineal integrity and a decrease of at least 14% in severe perineal trauma, with

Table 1. Hyaluronidase Injections in the Perineum During Vaginal Birth: Description and Results of 10 Studies

Study, Year, Location	Type of Study, Eligibility, Study Sample	Intervention and Control (if Applicable)	Main Results/Comments
Digonnet et al[10] 1952, France	Case series, descriptive study; spontaneous birth; all nulliparous, N = 67	10 SU[a] HAase (Kinetin) + 6 mL saline solution injected into the 2 sides of the perineal body before complete dilation	Perineal softening comparable to that of multiparous women; original perineal consistency recovered after 24 h; no complication after injection; no information concerning frequency of episiotomy and lacerations
Frenzel[11] 1954, Germany	Case series, descriptive study; both spontaneous birth and forceps birth; group 1: n = 44 primiparous (3 forceps), group 2: n = 8 multiparous	10 SU[a] HAase (Kinetin) + 10 mL saline solution or 10 mL 1% procaine injected into subcutaneous tissue into the 2 sides of the perineal body about 15 min before fetal expulsion; no information about which women received HAase reconstituted with saline solution or with 1% procaine	Group 1: 1st degree laceration, 16%; 2nd degree laceration, 3%; episiotomy, 3%; group 2: intact perineum, 100%
Mink[12] 1955, Germany	Open, controlled trial; both spontaneous birth and forceps birth; all primiparous, intervention group: n = 117 (6 forceps), control group: n = 239 (9 forceps)	Intervention group: 10 SU[a] HAase (Kinetin) + 2-6 mL 0.5%-1% procaine injected into the 2 sides of the perineal body after complete dilation; control group: no injection	Intervention group: intact perineum, 75.2%; laceration, 19.6%; episiotomy, 5.2%; control group: intact perineum, 46.9%; laceration, 27.2%; episiotomy, 25.9%
Rimbach and Griefahn[13] 1955, Germany	Case series, descriptive study; spontaneous birth; no information about parity, N = 100	10-25 VRE[a] HAase (Hyason or Hylase) + 2-3 mL saline solution or 5 mL 0.5% procaine injected into the 2 sides of the perineal body about 5-20 min before fetal expulsion; initially HAase was reconstituted with saline solution, but this was changed to reconstitution with 0.5% procaine because women complained of pain during the injection	Intact perineum, 46%; vaginal and labial laceration, 26%; 1st and 2nd degree lacerations, 14%; episiotomy, 14%
Patrini[14] 1956, Italy	Case series, descriptive study; spontaneous birth; all nulliparous, N = 96	200 IU[a] HAase (Vister); group 1: + 5 mL procaine, n = 46; group 2: + 6 mg tubocurarine, n = 50 injected into the 2 sides of the perineal body about 15 min before fetal expulsion	Group 1: 2nd degree laceration, 11%; episiotomy, 2%; group 2: 2nd degree laceration, 40%; episiotomy, 4%; no complications after injection; perineal relaxation noted from 15 min to about 1 h after injection; less favorable outcomes in group 2 from competitive antagonism between HAase and curare (tubocurarine)

continued

Table 1. Hyaluronidase Injections in the Perineum During Vaginal Birth: Description and Results of 10 Studies

Study, Year, Location	Type of Study, Eligibility, Study Sample	Intervention and Control (if Applicable)	Main Results/Comments
Petronio[15] 1956, Italy	Case series, descriptive study; spontaneous birth; group 1: n = 100 nulliparous, group 2: n = 200 multiparous	100 UVC[a] HAase (Cilag) + 8 mL saline solution injected into the 2 sides of the perineal body	Group 1: perineal trauma, 27% (laceration, 25%; episiotomy, 2%); group 2: perineal trauma, 16% (laceration, 15%; episiotomy, 1%); reduction of 31 percentage points in perineal trauma in nulliparous and 32 percentage points in multiparous (rate of perineal trauma in institution was 58% in nulliparous and 48% in multiparous); no complications after injection
Roncuzzi[16] 1957, Italy	Case series, descriptive study; both spontaneous birth and forceps birth; group 1: n = 80 nulliparous (8 forceps), group 2: n = 20 multiparous	500-750 USPU[a] HAase + 10 mL 2% procaine injected into the 2 sides of the perineal body below the fourchette and lower third of the labia majora about 10 min after birth	Intact perineum, 73% (group 1, 68.7%; group 2, 90%); increase of 35 percentage points in intact perineum (rate of intact perineum in nulliparous and multiparous in institution was about 38%)
O´Leary and Erez[17] 1965, United States	Open, randomized controlled trial; both spontaneous birth and forceps birth; both nulliparous and primiparous, intervention group: n = 50 (23 forceps, 15 nulliparous), control group: 50 (21 forceps, 10 nulliparous)	Intervention group: 750-1550 TRU[a] HAase (Wydase), 5-10 mL prepared HAase injected into the perineal body, hymen, and any previous episiotomy scars prior to birth; control group: no injection; perineal relaxation graded on a scale of 0-4+ (0, no relaxation; 1+, very little; 2+, moderate; 3+, very good; 4+, marked relaxation)	Intervention group: 88% marked or very good perineal relaxation after 3-4 min after injection (perineal tissues became softened, pliable, and relaxed); intact perineum, 60%; 1st degree laceration, 2%; 2nd degree laceration, 1%; episiotomy, 36%; control group: intact perineum, 20%; 1st degree laceration, 6%; 2nd degree laceration, 6%; episiotomy, 68%; good or satisfactory perineal support 3-4 d and 6 wk after in both groups
Chatfield and Moir[18] 1966, United Kingdom	Blinded, randomized controlled trial; spontaneous birth; all nulliparous, intervention group: n = 57, control group 1: n = 66, control group 2: n = 77	Intervention group: 1500 USPU[a] HAase (Hyalase) + 5 mL saline solution; control group 1: 5 mL saline solution injected into the perineal body, base of the hymen, and fourchette at onset of second stage of labor; control group 2: no injection	Intervention group: intact perineum, 35.1%; episiotomy, 54.3%; control group 1: intact perineum, 21.2%; episiotomy, 53%; control group 2: intact perineum, 22.1%; episiotomy, 58.4%; no statistically significant difference; no adverse effects at 6 d and 6 wk after birth
Scarabotto and Riesco[19] 2008, Brazil	Open, randomized controlled trial; spontaneous birth; all nulliparous, intervention group: n = 71, control group: n = 68	Intervention group: 20,000 TRU[a] HAase (Hyalozima) + 5 mL sterile water injected into the 2 sides of the perineal body and fourchette at onset of second stage of labor; control group: no injection	Intervention group: intact perineum, 60.6%; 1st degree laceration, 33.8%; episiotomy, 5.6%; no women with 2nd degree lacerations; control group: intact perineum, 23.5%; 1st degree laceration, 61.8%; 2nd degree laceration/episiotomy, 14,7%; HAase was a protective factor against perineal trauma, with statistically significant difference between groups

Abbreviations: HAase, hyaluronidase; IU, international unit; SU, Schering unit; TRU, turbidity-reducing unit; USPU, United States Pharmacopeia unit; UVC, unità di viscosità Cilag; VRE, viskositätssenkenden einheiten.
[a]The amount of HAase is given in the unit reported by each author.

5% significance (by Bonferroni's criterion).[21] To achieve 90% power, the required sample size was 76 women per group (experimental and control).

Procedures and Perineal Management

Independent pharmacists from the laboratory produced both HAase and the placebo and dispensed flasks according to a computer-generated randomization list. The flasks were identified by using a code number, and this information was not revealed until the end of data collection.

Each flask of HAase (Hyalozima; Apsen Farmacêutica SA, São Paulo, Brazil) contained 20.000 turbidity-reducing units plus sodium chloride (active stabilizer) plus mannitol (diluent) plus thiomersal (preservative), and each flask of the placebo contained sodium chloride (active stabilizer) plus mannitol (diluent) plus thiomersal (preservative) plus benzalkonium chloride (preservative sparkling) plus riboflavin phosphate (dye).

The flask of lyophilized HAase or placebo powder was reconstituted with sterile water by using a 5-mL syringe, and the solution was injected (26-gauge 1/2-inch needle) immediately after reconstitution. Both HAase and placebo had the same appearance before and after reconstitution, with pH values between 4.5 and 6.5.

During the second stage of labor, each participant was asked to remain in a semisitting position in a birthing bed, and the perineum was washed prior to birth by using a neutral liquid soap. Following this, the solution was injected through the perineal subcutaneous tissue, with 1 mL injected in the center of the perineum and 2 mL in each of the sides (left and right). The needle was introduced in the fourchette down toward the anus and was pulled back and angled in the diagonal direction to get the lateral portions of the perineal body in the shape of a fan. Following injection, no further manipulation of the perineal region was done, such as massage or lateral or inferior distension.

Maneuvers designed to protect the perineum were used during crowning, expulsion, and rotation of the fetal head. These maneuvers consisted of maintaining the palm of the hand in the posterior perineum region and applying moderate pressure to the perineum while the fetal head was emerging. Concomitantly, the fingers of the other hand were used to support the anterior region of the perineum, controlling the flexion of the fetal head and bilaterally supporting the ischiocavernosus and bulbocavernosus pelvic muscles, the urethral meatus, and the labia minora and majora.

After the expulsion of the fetal head, the palm of the hand continued to provide pressure to the posterior perineum region in order to support it, waiting for the spontaneous external rotation and expulsion of the shoulders. If this did not occur, a maneuver involving holding the fetal head was used to rotate it, then the anterior shoulder was pulled downward and subsequently gentle traction was applied upward to ease expulsion of the posterior shoulder.

The mother was given the option of laboring without directed pushing. Instructions for directed pushing were given only in cases in which the fetal heart rate was not reassuring during the expulsion period or when spontaneous contractions were insufficiently strong to effect birth.

When episiotomy was indicated for either perineal rigidity or a need to abbreviate the time to birth, it was performed after an initial dose of 10 mL of 1% lidocaine chlorohydrate solution without epinephrine was injected into the perineum.

Suturing the laceration was initiated after the administration of local anesthesia with an initial dose of 1 to 5 mL of 1% lidocaine chlorohydrate solution with epinephrine, according to the degree of laceration, and was supplemented with more if necessary to reduce pain during the repair.[22]

Data Collection

Data were collected from January to June 2009, in 2 stages: during labor and in the postpartum period (1-2 h and 24-48 h after birth). Birth and postpartum evaluations were conducted by the researchers and a team of 3 nurse-midwives, according to the research protocol. Perineal assessment at birth included classification of the degree of laceration and measurements of its length and depth, with use of the Peri-Rule. The postpartum vulvoperineal inspection was conducted to assess the condition of the perineum following birth as well as to evaluate any possible complications including edema, hyperemia, ecchymosis, dehiscence, or secretion. Information regarding the details of labor, birth, health of the newborn, and the postpartum condition of the perineum was recorded.

The primary outcomes of the study—integrity or perineal trauma and its severity—were assessed independently by the midwife who attended the birth and by a midwife-judge, immediately after fetal expulsion. The midwife-judge was a nurse-midwife from the birth center staff who was on duty at the time of birth.

Before we started data collection, a preliminary study was conducted to evaluate potential bias in the classification of perineal lacerations following spontaneous births among the researcher and nurse-midwives working as judges. It revealed a need to train the team and the midwife-judges to assess perineal trauma according to the protocol defined for the research prior to the start of data collection. Following this, the researchers offered a theoretical and practical program to train the nurse-midwives to carry out all stages of data collection (ie, enrollment, procedures, perineal assessment, reporting). Moreover, after the training, a new protocol for perineal trauma assessment was implemented in the birth center.

Data Analysis

Data were recorded by using MS Office Excel (Microsoft Corporation, Redmond, WA). The descriptive analysis included the calculation of absolute and relative frequencies of categorical variables and the mean, standard deviation (SD), and minimum and maximum values of continuous variables. A 1-tailed Fisher exact test was used for statistical analysis, with a value of $P < .025$ (by Bonferroni's criterion) considered significant. Analysis was complemented with the calculation of measures of effect—absolute risk reduction with its confidence interval (CI) of 95% and the number needed to treat (NNT). Data processing was performed by Minitab for Windows, version 15.1.20.0.

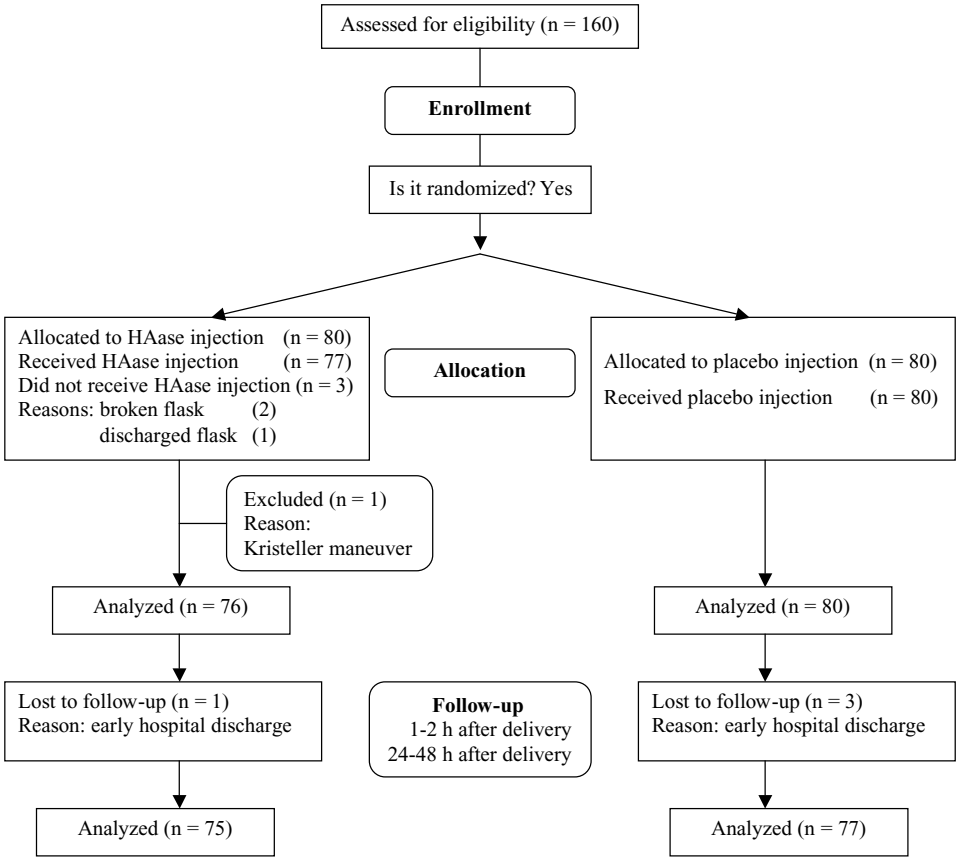

Figure 1. Flow Diagram of Trial Participants (HAase, Hyaluronidase)

RESULTS

From January to February 2007, when this study was planned, the records concerning 2077 births indicated that 78.9% were vaginal births. In this period, in 901 women without previous vaginal birth, the perineal outcomes were: episiotomy 39.6%, intact perineum 27.6%, first-degree laceration 24.6%, second-degree laceration 7.9%, and third-degree laceration 0.3%.

A total of 160 women who met the inclusion criteria were recruited and enrolled in the study. None of them declined to participate, and 4 were excluded for the following reasons: 3 did not receive the intervention (2 flasks were broken during use, and 1 was discarded because of accidental introduction of a fragment of the rubber lid during the aspiration of the solution); the fourth was excluded because the providers conducted uterine fundal pressure to help birthing (Kristeller maneuver), and it is thought that this maneuver is not standard and may increase perineal trauma. The final sample consisted of 156 participants distributed into 2 groups, with 76 women in the experimental group and 80 in the control group. Because of earlier hospital discharge, the perineal assessment between 24 hours and 48 hours was not performed in 4 women (Figure 1).

The average age of the participants was 22.5 years (4.5) and ranged from 18 to 38 years. Details regarding age, ethnicity, education, partner, and newborn weight are summarized in Table 2. The average (SD) birth weight was 3151 g (395) (3216 g [427] and 3175 g [363] in the experimental and control groups, respectively). The homogeneity of the groups for the sociodemographic maternal variables and newborn birth weights was established by the randomized allocation of the women into the groups.

Almost all of the newborns in both groups had Apgar scores of greater than or equal to 7 in the first and fifth minutes of life (94.2% and 99.4%, respectively). The 2 newborns with 5-minute Apgar scores equal to 6 recovered and remained with the mothers at rooming-in until hospital discharge.

The perineal outcomes are summarized in Table 3. Perineal integrity occurred in 34.2% of the experimental group and 32.5% of the control group, which was not a statistically significant difference ($P = .477$). Where perineal integrity was assessed, the women with intact perineums and those with perineal trauma (ie, categorized as women with episiotomies deemed first-degree, second-degree, and third-degree lacerations) were analyzed separately.

In order to test the hypothesis that the use of HAase reduces severe perineal trauma (ie, episiotomy, second-degree, and third-degree lacerations), the women with first-degree lacerations and those with intact perineums were grouped together. The comparative analysis indicated that severe perineal trauma occurred in 28.9% of the experimental group and 38.8% of the control group, which also was not a statistically significant difference ($P = .131$).

Table 2. Characteristics of Mothers and Newborns (N = 156)

Characteristic	Experimental Group, n (%)	Control Group, n (%)
Maternal age, y		
< 20	23 (30.3)	24 (30.0)
20-24	37 (48.6)	36 (45.1)
25-29	10 (13.2)	10 (12.5)
30-34	4 (5.3)	9 (11.2)
≥ 35	2 (2.6)	1 (1.2)
Race		
Not white	49 (64.5)	47 (58.7)
White	27 (35.5)	33 (41.3)
Education level completed		
Elementary	16 (21.1)	20 (25.0)
Secondary	60 (78.9)	60 (75.0)
Conjugal status		
With partner	57 (75.0)	62 (77.5)
Without partner	19 (25.0)	18 (22.5)
Birth weight, g		
< 2500	6 (7.9)	1 (1.3)
2500-2990	22 (28.9)	20 (25.0)
3000-3490	36 (47.5)	45 (56.2)
3500-3990	9 (11.8)	12 (15.0)
≥ 4000	3 (3.9)	2 (2.5)

In both analyses, because the 95% CI for the absolute risk reduction extends from a negative number (treatment may harm) to a positive number (treatment may benefit), it is difficult to compute a 95% CI for the NNT in these cases, and we cannot say with 95% certainty whether the intervention is harmful, has no effect, or is helpful compared with the control.[23]

Episiotomy was performed in 11 women. The indications for intervention were: 1) a shortened second stage of labor (7 instances), 2) a rigid perineum (5 instances, 1 in the experimental group and 4 in the control group), and 3) macrosomic fetus (3 instances). In some circumstances, more than 1 indication was present. Four women in the control group had third-degree lacerations (level 3a), and no women in the experimental group had a third-degree laceration. When considering women with any type of perineal trauma, first-degree laceration was the most common in both groups, and it occurred in 56% of the experimental group and 42.6% of the control group.

Most women adopted exclusively spontaneous pushing; in these cases, the proportion of perineal integrity was above 71% in both groups. When directed pushing was adopted, the proportion of severe perineal trauma was lower among women who received injections of HAase. Details concerning the type of perineal trauma and bearing down efforts are presented in Table 3.

Considering that the design of the study and the sample size were developed exclusively to test a specific hypothesis, the inferential analysis was not performed, and *P* values were not calculated for the type of perineal trauma based on spontaneous and directed pushing variables.

The depth and length of perineal lacerations, measured in centimeters with the Peri-Rule, are presented in Table 4.

In the period between 1 and 2 hours after birth, 54% and 52.5% of the experimental and control groups, respectively, had perineal edema. However, between 24 and 48 hours later, this ratio was reduced to 12% in the group that received HAase and to 29.9% in the group that received placebo solution. There were 3 cases of hematoma with application of placebo and 1 with the enzyme.

Concerning perineal pain, 48.7% and 45% in the experimental and control groups, respectively, reported pain during injection of HAase and placebo. Ice packs were placed on the perineum immediately after birth in 26.9% of participants (22.4% and 31.2% in the experimental and control groups, respectively). This perineal care was applied in cases of severe edema, hematoma, or local pain.

DISCUSSION

Studies on the use of HAase in childbirth from the 1950s and 1960s found that HAase injections into the perineum had a protective effect in the perineal region. Several studies are only descriptive and were conducted in French, German, and Italian hospitals. In most of these services, the perineal trauma rates were low, and episiotomy rates were below double digits (varying from 0.5%–25.9%).[10–16] Nevertheless, the blinded RCT conducted by Chatfield and Moir,[18] which had 2 control groups (with saline injection and without any injection) and an experimental group using HAase found no statistically significant difference regarding perineal outcomes.

The results of the present study did not show a statistically significant difference in perineal integrity between the experimental and control groups (34.2% vs 32.5%, respectively). Despite a lower proportion of second-degree and third-degree lacerations and episiotomy in the experimental group compared with the control group (28.9% vs 38.8%, respectively), this difference is not statistically significant.

These results contrast with those of Scarabotto and Riesco,[19] who found perineal integrity in 60.6% of 71 women in the experimental group and 23.5% of 68 women in the control group, with a statistically significant difference between the groups. Second-degree lacerations and episiotomy occurred among 14.7% of women in the control group, and none who received HAase had second-degree lacerations, although episiotomy was performed in 4 of them (5.6%).

Despite using the same injection technique and HAase dose in both studies, differences in design and procedures may explain the divergent findings. Although the pilot study was randomized and controlled, there was no masking of intervention and outcome, producing a possible bias in the evaluation. The use of oxytocin and the birth position, reported as factors related to perineal trauma,[5,7] were other important differences between the 2 studies.

In this research, HAase and placebo were administered in injectable form. Therefore, not only could HAase have acted in the perineal tissue but also some local transient effect may

Table 3. Perineal Outcomes, Type of Perineal Trauma, and Spontaneous or Directed Pushing During Second Stage of Labor

Variable	Experimental Group, n (%)	Control Group, n (%)
Perineal outcome (N = 156)[a]		
Intact perineum	26 (34.2)	26 (32.5)
Episiotomy or 1st-, 2nd-, or 3rd-degree laceration	50 (68.8)	54 (67.5)
Perineal outcome (N = 156)[b]		
Intact perineum or 1st-degree laceration	54 (71.1)	49 (61.2)
Episiotomy or 2nd- or 3rd-degree laceration	22 (28.9)	31 (38.8)
Type of perineal trauma (n = 104)		
1st-degree laceration	28 (56.0)	23 (42.6)
2nd-degree laceration	19 (38.0)	19 (35.2)
3rd-degree laceration	0	4 (7.4)
Episiotomy	3 (6.0)	8 (14.8)
Spontaneous pushing (n = 103)		
Intact perineum and 1st-degree laceration	34 (72.3)	42 (71.2)
Episiotomy or 2nd- or 3rd-degree laceration	10 (22.7)	17 (28.8)
Directed pushing (n = 53)		
Intact perineum and 1st-degree laceration	20 (62.5)	7 (33.3)
Episiotomy or 2nd- or 3rd-degree laceration	12 (37.5)	14 (66.7)

Abbreviations: ARR, absolute risk reduction; CI, confidence interval; NNT, number needed to treat.
[a] $P = .477$ (1-tailed Fisher exact test); ARR (95% CI) = −0.017 (−1 to 0.107); NNT = 59.
[b] $P = .131$ (1-tailed Fisher exact test); ARR (95% CI) = −0.098 (−1 to 0.26); NNT = 11.

have occurred due to the infiltration of 5 mL of placebo solution, increasing the tissue fragility and the odds of laceration.

It is important to consider that even when the results of an intervention are favorable and are supported by well-designed studies with appropriate statistical analysis, clinical significance must be analyzed; in addition, it is also worthwhile to distinguish between the benefits and the unwanted effects of the intervention.[24] Accordingly, measures of effect are necessary to evaluate the impact of an intervention, and 1 of them is the NNT. This measure represents the number of patients required to receive treatment in order to achieve a protective effect. It would indicate not only that there may be benefits from the intervention but would also indicate that when calculating an NNT when the CI crosses zero it is possible that the treatment could result in harm. In this case, 59 women would need to receive the intervention to result in one woman with intact perineum and 11 women would be required to prevent episiotomy and 2nd- or 3rd-degree lacerations due to the use of HAase. The results indicate that it may be necessary to treat a very large number of women to achieve a protective effect and avoid perineal trauma. Furthermore, HAase is a pharmacological substance that involves cost inherent in the process of production, marketing, control, and administration.

The study was designed with episiotomy and spontaneous second-degree, third-degree, and fourth-degree lacerations grouped together, because in each of these situations layer tissues are affected. Likewise, the randomization and blinding of the study minimizes any bias, although an episiotomy is a procedure performed according to the practice and decision of the professional who attended the birth.

First-degree lacerations that occur throughout the vulvoperineal region are considered minor trauma and have good clinical resolution, and most of them do not need sutures unless they are actively bleeding. Among women in both groups, this trauma was the most frequent (56% and 42.6% in the experimental and control groups, respectively), and because women in this study were primiparas, this result is plausible from a clinical point of view, because studies have shown that there is a greater probability of perineal trauma in primiparous women.[2,3,25]

It is important to note that the rate of episiotomy of 7% obtained in this study is among the lowest conducted in primiparous women, according to several studies.[26–28] Although it is not possible to use any statistical inference analysis, given the low prevalence, it is worth noting that all third-degree lacerations and 8 of 11 episiotomies were in the control group, indicating a possible protective effect of HAase.

Spontaneous pushing may be a protective factor regarding perineal lacerations; a clinical trial with 1176 pregnant women showed that the sole advantage of directed pushing is to shorten the second stage of labor. Although pushing is required in some instances, it is seen as a disadvantage to the integrity of the perineum because of the increased risk of perineal trauma. Because of this, pushing is considered a predictor of sutured trauma in first vaginal births.[1] In the present study, spontaneous pushing also was a protective perineal factor. Among all the 103 women who pushed spontaneously, only 26% had severe perineal trauma, regardless of the type of solution injected into the perineum. On the other hand, of the 53 women who had directed pushing, 16 (49%) had severe perineal trauma (37.5% in the experimental group and 66.7% in the control group).

Perineal trauma often produces discomfort or pain that persists after birth. It also may cause morbidities, such as edema, hematoma, and infection that are associated with instrumental birth, episiotomy, severe lacerations, techniques, and material used for suturing perineal lacerations. The perineal conditions of the studied women showed that the primary morbidity after childbirth was edema, which markedly declined over the first 48 hours, as shown in other studies on injection of HAase.[10,15,17–19]

In Brazil, midwives have been trained to assist births without routine episiotomy only within the last decade. This implies that the professionals must be trained not only to prevent perineal trauma but also to properly evaluate spontaneous lacerations.[29]

Anatomic individual details in the vulvoperineal region of each woman can interfere with the classification of perineal lacerations. Tissue thickness, tonality, and bleeding of

the perineal region are factors that can influence this assessment. Typically, there is concern among nurses and midwives to produce as little damage as possible to the woman. This can lead to the tendency of professionals who attend childbirth to underestimate the degree of laceration. However, the correct assessment of lacerations is crucial for appropriate conduct in repairing lacerations, giving postpartum care, and preventing morbidity. Therefore, the assessment of the laceration degree becomes a challenge to midwifery practice.

As shown in the Methods section, nurse-midwives who attended the births were trained to assess perineal trauma in order to standardize the classification and measurement of perineal lacerations. The procedure was performed with the Peri-Rule, measuring the depth of muscle injury and the length of the mucosa and skin injury.

The Peri-Rule was developed and tested in a study conducted in the United Kingdom between 2000 and 2001. In this study, the Peri-Rule was used to measure perineal trauma among 130 women who had vaginal births. The authors recognized the complexity of evaluating second-degree lacerations that are poorly defined and show variation in length and depth. They concluded that there was bias in perineal trauma classification and recommended assessment protocols and that tools for easy clinical application should be adopted.[30]

In this study, the homogenization of perineal laceration classification was essential to ensure the consistency of results, considering that the nurse-midwives who attended childbirth as well as the midwife-judges participated in the assessment of perineal outcomes.

Clinical trials are designed to test the safety, efficacy, and effectiveness of new treatments and the appropriate doses. The control, randomization, and masking of tests ensure the minimization of bias. When these are done in a double-blind study, the groups are blinded to the intervention received. But if the intervention cannot be masked, the outcome should be blinded, with 1 observer who does not know which patients received the intervention.[31]

These methodological aspects are essential, and besides the use of oxytocin during childbirth and the maternal position at birth, may explain the main difference in the results of the pilot study and the present research.

To obtain reliable results in an RCT, a well-designed pilot study should be performed prior to the main research in order to provide information about feasibility, planning, and justification. For a pilot study to be successful, it is necessary that the assumptions and the main objectives of the research are clear, so that it can lead to changes in research design, encouraging methodological rigor. It is also recommended that the analysis of the pilot study be essentially descriptive and that the tendency not to continue with the main research should be avoided even if the expected results were not found by the pilot study.[32] In addition, a pilot study can guide the researcher regarding ethical aspects of the research. When a professional believes beforehand that the intervention being proposed is the best, the concept of equipoise, an ethic term applied in epidemiology and health that means balance, must be considered to avoid research bias.[33]

Thus, 1 of the main considerations of the present study, with implications for research and practice, is reaffirmation of the importance of pilot studies and clinical trials well designed and properly conducted to improve midwifery and nursing evidence-based practice.

Table 4. Depth and Length of Perineal Lacerations (n = 93)

Depth and Length of Lacerations (cm)	Experimental Group, mean (SD)	Control Group, mean (SD)
1st-degree laceration (n = 51)		
Depth	0.3 (0.4)	0.4 (0.5)
Length of mucosa	1.6 (0.1)	2.0 (1.2)
Length of skin	0.3 (0.7)	0.6 (1.0)
2nd-degree laceration (n = 38)		
Depth	1.9 (1.0)	2.3 (1.2)
Length of mucosa	3.4 (1.4)	3.5 (1.2)
Length of skin	2.0 (1.3)	2.5 (1.3)
3rd-degree laceration (n = 4)		
Depth	–	2.4 (0.7)
Length of mucosa	–	3.9 (1.4)
Length of skin	–	4.5 (1.0)

CONCLUSION

The results showed that there was no increase in the proportion of perineal integrity nor reduction of the proportion of severe perineal trauma with HAase injection in the perineum. Thus, the hypothesis that HAase increases the proportion of perineal integrity and reduces the proportion of severe perineal trauma during birth was not confirmed.

ACKNOWLEDGMENTS

This work was supported by the State of São Paulo Research Foundation. We would like to thank study participants, both women and nurse-midwives, Apsen Farmacêutica, Laboratório Cristália (São Paulo, Brazil), and Peri-Rule (University of Birmingham, United Kingdom).

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