ISSN 0857-6084

THAI JOURNAL OF OBSTETRICS AND GYNAECOLOGY

THE OFFICIAL JOURNAL OF
THE ROYAL THAI COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

VOL. 26 NO. 3 JULY - SEPTEMBER 2018

Executive Board
of
The Royal Thai College of Obstetricians and Gynaecologists

PRESIDENT

Prof. Pisake Lumbiganon, M.D.

PRESIDENT-Elect

Air Marshal Dr. Karun Kengsakul, M.D.

VICE PRESIDENT

Dr. Pisanu Kantipong, M.D.

SECRETARY GENERAL

Prof. Sarikapan Wilailak, M.D.

DEPUTY SECRETARY GENERAL

Assoc. Prof. Ruangsin Chawarat, M.D.

TREASURER

Dr. Suwanna Asavapiriyanont, M.D.

EXECUTIVE BOARD MEMBERS

Assoc. Prof. Boonsri Chanrachakul, M.D.
Assoc. Prof. Dittakarn Borriboonhiransan, M.D.
Assoc. Prof. Ekachai Kovavisarach, M.D.
Prof. Kovit Khampitak, M.D.
Assoc. Prof. Mongkol Benjapibal, M.D.
Prof. Ounjai Kor-Anantakul, M.D.
Assoc. Prof. Saknan Manotaya, M.D.
Assoc. Prof. Suphakde Julavijitphong, M.D.
Assoc. Prof. Suvit Bunyavejchevin, M.D.
Assoc. Prof. Unnop Jaisamrarn, M.D.
Prof. Vorapong Phupong, M.D.
Dr. Wisit Supakarapongkul, M.D.

Thai Journal of Obstetrics and Gynaecology

ISSN : 0857-6084. The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

Manager: LUMBIGANON Pisake
Assistant Manager: PHAUNGMALEE Arissara
Office: 8th Floor, The Royal Golden Jubilee Bldg. 2, Soi Soonvijai, New Petchburi Road, Bangkapi, Bangkok 10310, Thailand
Published by: PIMDEE Co., Ltd. Tel: 0-2874-4401, 086-144-8500

Website: www.tci-thaijo.org/index.php/tjog, E-mail: Vorapong.P@chula.ac.th

Aim and Scope of the Thai Journal of Obstetrics and Gynaecology (Official journal of the Royal Thai College of Obstetricians and Gynaecologists (RTCOG)

Thai Journal Obstetrics and Gynaecology is the official journal of The Royal Thai College of Obstetricians and Gynaecologists. This is a double-blind peer-reviewed journal aiming to promote academic knowledge and provide a forum for publication in Obstetrics and Gynecology. Manuscripts submitted to Thai Journal Obstetrics and Gynaecology will be accepted on the understanding that the author must not have previously submitted the paper to another journal or have published the material elsewhere.

Type of Paper: Original article, Case report, Meta-analysis, Review article, Letter to editor
Specialty of Paper: General obstetrics, General gynaecology, Reproductive medicine, Maternal-fetal medicine, Gynaecologic oncology, Urogynaecology
Frequency: 4 issues per year (January-March, April-June, July-September, October-December)
Language: Fulltext in English, Abstract both in Thai and English
Thai-Journal Impact Factor: 0.072 average since 2013-2015
Free Access: online

Direction to contributors. All papers should be sent to Editor, Thai Journal of Obstetrics and Gynaecology, 8th Floor, The Royal Golden Jubilee Bldg. 2, Soi Soonvijai, New Petchburi Road, Bangkapi, Bangkok 10310, Thailand. The editorial board will decide upon the time of publication and retain the right to modify the style and the length of the contribution. However, major changes will be agreed with the authors.

Manuscripts. All manuscripts can be submitted online (http://tci-thaijo.org/index.php/tjog) along with a cover letter, author agreement form and the checklist guideline. A cover letter must include name of the corresponding author, full address, telephone number, fax number, and e-mail address, title and category of the submitted manuscript: original article, case report or review articles. Authors for whom English is a second language may choose to have their manuscript professionally edited before submission to improve the English.

The requirements for manuscripts submitted to Thai Journal of Obstetrics and Gynaecology conform to the UNIFORM REQUIREMENT FOR MANUSCRIPTS SUBMITTED TO BIOMEDICAL JOURNALS established by the international committee of medical journal editor which published in N Engl J Med 1991;324:424-8 and BMJ 1991;302:338-41.

Manuscripts of original work should be arranged in the conventional order of title page, abstract, keywords, introduction, materials and methods, results, discussion, acknowledgments, references, table and figure legends.

Manuscripts of research article, case report and review article (without author's name) will be reviewed by two reviewers. Editor in chief will make the final decision in case of discrepancy of reviewer's opinion. The editorial board has the right to grammatically correct any content and has all right preserved to consider and to publish any article.

All published manuscripts are properties of Thai Journal of Obstetrics and Gynaecology. The content and any opinions in the published papers are the sole responsibility of the authors, not the editorial board.

Title page. The title page should contain the title, which should be concised and informative, the authors' name with the highest academic degree, and address of the authors including the correspondence.

Abstract. A structured abstract, with 250 words or less, is submitted as required for regular articles. The abstract should state the Objective, Materials and Methods, Results, and Conclusions, each with a brief adequate presentation. Abstracts for case reports should not exceed 50 words.

Keyword. Below the abstract list 3 to 5 keywords or short phrases for indexing purposes.

Introduction. State clearly the purpose of the study. Summarize the rationale for the study. Give only strictly pertinent references and it is not necessary to include all the background literature.

Materials and Methods. Describe briefly the plan, patients, procedures, controls and statistical method employed.

Results. Present your results in sequence in the text, tables, and illustrations. Summarize and emphasize only important observations.

Discussion. Comment on your results and relate them to those of other studies. Recommendations may be included.

References. References to the literature should be numbered consecutively and indicated by a superscript in parenthesize. Identify references in the text, tables and legends by arabic numerals within marks. Cite the names of all authors when there are six or fewer; when seven or more list the first six followed by et al. Names of journals should be abbreviated in the style used in *Index Medicus*. Try to avoid using abstracts as references. Unpublished data and personal communication should not be used as references.

Example of references:

Journal article

Phupong V, Aribarg A. Congenital arteriovenous malformations of the uterus. Thai J Obstet Gynaecol 2000;12:67-70.

Book

Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams Obstetrics. 23rd ed. New York: McGraw-Hill, 2010: 804-31.

Chapter in a Book

Phupong V. Management of PPROM AT 32 to 34 weeks. In: Desai SV, Tank P, eds. Handbbok on preterm prelabor rupture of membranes in a low source setting. New Delhi: Jaypee Brothers Medical Publishers Ltd, 2012: 39-46.

Tables. Tables should present new information rather than duplicating what is in the text. Please supply editable files. A short descriptive title should appear above each table with a clear legend and any foonotes suitably identified below. All units must be included.

Figures. Figures should be high quality (1200 dpi for line art, 600 dpi for gray scale and 300 dpi for colour). Figures should be saved as TIFT or JPEG files. Figures should be completely labelled, taking into account necessary size reduction. Captions should be typed, double - spaced, on a separate sheet.

Ethical consideration. Each author's contribution to the paper is to be quantified. Authors must state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken.

Publication Ethics and Publication Malpractice Statement. The publication ethics is required for publication in *Thai J Obstet Gynaecol*. The publication ethics guidelines are followed the *Committee on Publication Ethics-COPE (http://publicationethics.org/)*.

Editor of Thai Journal of Obstetrics and Gynaecology

1. strive to meet the needs of readers and authors, constantly improve the journal.

2. have processes in place to assure the quality of the material published.

3. give timely and comprehensive feedback to authors.

4. maintain the integrity of the academic record and preclude business needs from compromising intellectual and ethical standards.

5. are willing to publish corrections, clarifications, retractions and apologies when needed.

6. seek the views of authors, readers, reviewers and editorial board members about ways of improving the journal's processes.

7. encourage and being aware of research into peer review and publishing and reassessing the journal's processes in the light of new findings.

8. endeavor to ensure that research published was carried out according to the relevant internationally accepted guidelines (e.g. the Declaration of Helsinki for clinical research, the AERA and BERA guidelines for educational research).

9. seek assurances that all research has been approved by an appropriate body (e.g. research ethics committee, institutional review board).

10. have a duty to act if editors suspect misconduct or if an allegation of misconduct is brought to editors.

11. pursue misconduct for the following reasons in published and unpublished work: plagiarism of other works, data fabrication and falsification, when a submitted manuscript has been found to be under revision elsewhere or published elsewhere, or where there is citation manipulation.

12. make decisions to accept or reject a paper for publication based on the paper's importance, originality and clarity, and the study's validity and its relevance to the remit of the journal.

13. respect requests from authors that an individual should not review their submission, if these are well reasoned and practicable.

Authors who submit articles to TJOG should

1. Report the research conducted in an ethical and responsible manner and comply with all relevant legislation.

2. Present the results clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

3. Strive to describe the methods clearly and unambiguously so that the findings can be confirmed by others.

4. Adhere to publication requirements that submitted work is original, is not plagiarized, and has not been published elsewhere.

5. Take collective responsibility for submitted and published work.

6. Confirm that the authorship of research publications should accurately reflect individuals' contributions to the work and its reporting.

7. Disclose funding sources and relevant conflicts of interest.

Reviewers of TJOG should

1. Only agree to review manuscripts for which they have the subject expertise required to carry out a proper assessment and which they can assess in a timely manner

2. Respect the confidentiality of peer review and not reveal any details of a manuscript or its review, during or after the peer-review process, beyond those that are released by the journal

3. Declare all potential conflicting interests, seeking advice from the journal if they are unsure whether something constitutes a relevant interest

4. Not allow their reviews to be influenced by the origins of a manuscript, by the nationality, religious or political beliefs, gender or other characteristics of the authors, or by commercial considerations

5. Be objective and constructive in their reviews, refraining from being hostile or inflammatory and from making libelous or derogatory personal comments

6. Acknowledge that peer review is largely a reciprocal endeavor and undertake to carry out their fair share of reviewing and in a timely manner

7. Provide journals with personal and professional information that is accurate and a true representation of their expertise

8. Recognize that impersonation of another individual during the review process is considered serious misconduct.

Article processing charge. To publish in Thai J Obstet Gynaecol, authors are required to pay an article processing charge (APC). The APC for all published papers is $100. Members of RTCOG have 50% discount for APC.

Subscription. Thai Journal of Obstetrics and Gynaecology is published every three months. The annual subscription rate is US$ 50 post free by surface mail. Order for subscription, business correspondences and advertising space should be addressed to the editor.

Thai Journal of Obstetrics and Gynaecology

ISSN 0857-6084

The Official Journal of the Royal Thai College of Obstetricians and Gynaecologists

Vol. 26 No. 3

JULY - SEPTEMBER 2018

CONTENTS

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No.3, pp. 141

EDITORIAL

This third issue of Thai Journal of Obstetrics and Gynaecology (TJOG) contains many interesting articles. The special article in this issue is "**Research Ethics in Obstetrics and Gynecology**".

RTCOG Annual Meeting 2018 will be held during 23-26 October 2018 at Dusit Thani Pattaya Hotel, Pattaya Beach Road, Pattaya City, Chonburi, Thailand. The theme of this meeting is "**Women's Health Care Sustainability**". This meeting will have AOFOG session on the topic "**Eradication of Invasive Cervical Cancer"**. All RTCOG members are cordially invited to participate this scientific meeting.

Residents who would like to publish their researches in TJOG should submit their works before October 1, 2018. Our editorial team and constructive reviewers will let them know the results before December 31, 2018.

Editor in Chief and managing staff already attended the Thai Journal Citation Index meeting: "**Powering your journal into the Web of Science Core Collection**" on July 13, 2018 at 10th Floor, The Knowledge Exchange: KX Building, Krung Thon Buri Rd, Khwaeng Bang Lamphu Lang, Thon Buri, Bangkok, Thailand. Editorial Board of TJOG prepare journal for submission to be index in Scopus index this year. Thus, there are many changes of the journal during this time.

Wish to see you at RTCOG Annual Meeting 2018 at Dusit Thani Pattaya Hotel, Pattaya Beach Road, Pattaya City, Chonburi, Thailand.

Prof. Vorapong Phupong, M.D.
Editor in Chief

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No.3, pp. 142-148

SPECIAL ARTICLE

Research Ethics in Obstetrics and Gynecology

Suthee Panichkul, M.D.,*.

** Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok 10400, Thailand*

ABSTRACT

Women should be presumed eligible to participate in obstetrics and gynecology studies. The potential for pregnancy should not automatically exclude a woman from participating in a study although the use of contraception may be required to participate. A significant concern in moving forward with enrolling pregnant women in research is that an intervention could cause harm to the fetus, and especially that the intervention or medication under study could cause a birth defect or other harms. Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies and their fetuses. When evidence concerning risks is unknown or conflicting, this must be disclosed to the pregnant or breastfeeding woman as part of the informed consent process.

Keywords: pregnancy, research ethics, informed consent, fetus

Correspondence to: *Suthee Panichkul, M.D., Department of Obstetrics and Gynecology, Phramongkutklao Hospital, Bangkok 10400, Thailand, Email address: sthpanich@hotmail.com*

Research Ethics in Obstetrics and Gynecology

Women must be included in health-related research unless a good scientific reason justifies their exclusion. Women have been excluded from much health-related research because of their child-bearing potential. As women have distinctive physiologies and health needs, they merit special consideration by researchers and research ethics committees. Only the informed consent of the woman herself should be required for her research participation. Since some societies lack respect for women's autonomy, in no case must the permission of another person replace the requirement of individual informed consent by the woman[1].

Guidelines for women who participate in clinical research[2]

1. Participation in clinical trials for women of reproductive age requires the capability of women to make their own choices, free of coercion, about healthcare as well as access to family planning.

2. Women of reproductive age are capable of making decisions about risks of potential teratogenicity as part of the decision-making around whether to participate in a clinical trial, and should be given their

choice. Even in the setting of no access to contraception or abortion, a woman's right to consider the risks of a clinical trial, in terms of teratogenicity and her own reproductive capacity, should belong with the woman.

3. Requirements to "prove" infertility with multiple pregnancy tests or proof through pathologic confirmation of hysterectomy or oophorectomy can raise psychological and practical barriers that discourage and can psychologically harm potential research subjects.

4. Consent to participate must always be the autonomous, informed choice of women of reproductive age.

5. A key benefit of inclusion is identifying potentially harmful side effects in a carefully controlled trial setting rather than after marketing and use where more women stand to be harmed before untoward side effects have been identified. Women have an equal right to the benefits (and harms) of research and to the knowledge gained that will inform better dosing and drug information after market entry.

Vulnerability of women

Despite the current general presumption that favors the inclusion of women in research, in many societies women remain socially vulnerable in the conducting of research. For example, they may suffer negligence or harm because of their submission to authority, their hesitancy or inability to ask questions and a cultural tendency to deny or tolerate pain and suffering[3]. When women in these situations are potential participants in research, researchers, sponsors and ethics committees must take special care in the research design, assessment of risks and benefits as well as the process of informed consent, to ensure that women have the necessary time and appropriate environment to make decisions based on information provided to them[4, 5].

When the research involves household surveys or interviews, researchers must take special care to ensure that the women are interviewed in a private place without the possibility of intrusion by other family members. In such studies, women must be given the option of conducting the interview in a setting of their choosing outside the home. Breach of confidentiality in these types of research could result in serious harms to women, even when the only information disclosed is their participation in the research. In studies involving women who have experienced gender-based violence, participation in interviews may cause emotional distress. Researchers must be prepared with referrals for psychological counselling if the need arises[1, 5].

Research involving pregnant women

Women of child-bearing potential must be informed in advance of the possibility of risks to the fetus should they become pregnant during their research participation. When participation in research might be hazardous to a fetus or a woman when she becomes pregnant, sponsors and researchers must guarantee access to pregnancy tests, effective contraceptive methods before and during the research and to a safe and legal abortion[6].

Research involving pregnant women presents specific scientific, ethical and legal complexities. The physiology of pregnancy changes dramatically across weeks, months and trimesters with complex feedback loops within and among the maternal body, placenta and fetus. Although trade-offs between maternal and fetal risks and benefits can introduce difficult challenges in study design, these are not in themselves a reason to exclude pregnant women. Several factors must be considered before pregnant women are excluded, including whether extrapolated knowledge from trials with pregnant animals and nonpregnant humans is available; whether the study offers the potential for direct benefit to the woman, her fetus or both and whether risks of inclusion already have been clearly established and minimized[6, 7].

A significant concern in moving forward with enrolling pregnant women in research is that an intervention could cause harm to the fetus, and especially that the intervention or medication under study could cause a birth defect or other harms. Although a cognitive bias exists toward considering the risks of intervention, including the risk of inclusion in research, a risk associated with failing to intervene and

exclusion from research also exists. Pursuit of zero risk to the fetus may come at a cost to the woman and the fetus and sets a standard that is not expected from parents enrolling infants and children in research. Maternal and fetal risks are deeply interconnected, and consideration of enrolling pregnant women in research requires balancing the risk of fetal harm with the potential for benefit and the importance of the information to be gained concerning the health of women and fetuses. Women of reproductive age have been directly excluded from research due to the concern of a potential of pregnancy in this age; indirectly by creating high barriers to inclusion with serial pregnancy testing and contraceptive requirements; and by cultural and legal barriers that preclude women of reproductive age from making decisions about their care including participating in clinical trials[6]. The consequences of this are significant as they result in drugs being used in populations where they have not been tested in, increasing the rate of drug reaction or failure as well as preventing access to new drugs that might prove lifesaving[7]. The arguments of fetal protection that exclude women of reproductive age question a woman's ability to make reasoned choices about fertility while on a clinical trial, reducing her rights to make choices about health care, reproduction and participation in clinical trials[7].

The inclusion of pregnant women in clinical research can be justified based on the reasons listed below.

1) The prospect of direct and indirect benefit to fetus

2) The imposition of no more than minimal risk for studies involving no prospect of benefit to fetus

3) A reasonable ratio of maternal benefit to fetal risk Tradeoffs between the fetus and the future child risk should be responsive to potential participants' values.

Although women of child-bearing age must be given the opportunity to participate in research, they must be informed that the research could include risks to the fetus when they become pregnant during the research. Access to a pregnancy test, to effective contraceptive methods and to a safe and legal abortion must be guaranteed before exposure to a potential teratogenic or mutagenic intervention[8-10]. When effective contraception and safe abortion are unavailable and alternative study sites are not feasible, the informed consent discussion must include information about the risk of unintended pregnancy, the legal grounds for abortion and information about reducing harms from unsafe abortion and subsequent complications. Also, when the pregnancy is not terminated, participants must be guaranteed a medical follow-up for their own health and that of the infant and child[10-12].

Regarding women who become pregnant during research, many biomedical protocols call for terminating the participation of women who become pregnant during the research. In cases where a drug or biological product is known to be mutagenic or teratogenic[13, 14], pregnant women must be removed from the study, and followed up and provided care through the duration of their pregnancy and delivery. Access to diagnostic tests must be provided to reveal any fetal anomalies. When anomalies are detected, women who wish may be referred for an abortion. When no evidence is found on the basis of which a potential harm to the fetus can be assumed, women who become pregnant should not automatically be removed from the study, but must be offered the option to continue or end their participation. For instance, in some cases it may be appropriate for a woman to stay in the study for safety monitoring but removed from the study drug. When the woman opts for continued participation, researchers and sponsors must offer adequate monitoring and support[1, 15].

Pregnant and breastfeeding women[1, 16]

Pregnant and breastfeeding women have distinctive physiologies and health needs. Research designed to obtain knowledge relevant to the health needs of the pregnant and breastfeeding woman must be promoted. Research among pregnant women must be initiated only after careful consideration of the best available relevant data.

For research interventions or procedures having

the potential to benefit either pregnant or breastfeeding women or their fetus or infant, risks must be minimized and outweighed by the prospect of potential individual benefit. For research interventions or procedures that have no potential individual benefits for pregnant and breastfeeding women:

1) the risks must be minimized and no more than minimal; and

2) the purpose of the research must be to obtain knowledge relevant to the particular health needs of pregnant or breastfeeding women or their fetuses or infants.

When the social value of the research for pregnant or breastfeeding women or their fetus or infant is compelling, and the research cannot be conducted among nonpregnant or nonbreastfeeding women, a research ethics committee may permit a minor increase above minimal risk[17, 18].

Short term and long term follow-up of the fetus and the child may be required in research involving pregnant and breastfeeding women depending upon the study intervention and its potential risks. As a general rule, health-related research involving pregnant women that has the potential to harm the fetus should be conducted only in settings where women can be guaranteed access to a safe, timely and legal abortion in the event that participation in the research makes the pregnancy unwanted[19].

Informed consent and risks and potential individual benefits

Researchers and research ethics committees must ensure that potential research participants are adequately informed about the risks to breastfeeding women and their infants, and about the risks to pregnant women (including future fertility), their pregnancies, their fetuses and their future offspring. Information must also include steps taken to maximize potential individual benefits and minimize risks[20, 21]. When evidence concerning risks is unknown or conflicting, this must be disclosed to the pregnant or breastfeeding woman as part of the informed consent process. She must be the one to make the final decision about the acceptability of these risks to her and her fetus or infant[22-25]. Women must also be informed the difficulty involved in determining causality in cases of fetal or infant abnormalities. Pregnant women may be recruited for research in which no prospect of potential individual benefit is available to them or the fetus only when the risks of the intervention are minimal. The involvement of pregnant women in research is complicated by the fact that it may present risks and potential individual benefits to the fetus as well as to the woman. Participation of breastfeeding women in biomedical research may similarly pose risks to the nursing infant. Research in pregnant and breastfeeding women must be initiated only after careful consideration of the best available data from preclinical research in pregnant animal models, research in nonpregnant women, retrospective observational studies and pregnancy registries[26-28].

In communities or societies where cultural beliefs accord more importance to the fetus than to the woman's life or health, women may feel constrained to participate or not to participate, in research. Special safeguards must be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of potential individual benefit to the fetus but not to the woman herself[26].

Patient perceptions of clinical research in pregnancy

The requirement for paternal consent in research with pregnant women does not mirror the requirement for dual-parent consent for research with children. Although fetal safety most commonly is seen as a reason to exclude pregnant women from research, this experience also speaks to the need to include pregnant women in research. Anything beyond a minimal risk; however, must be weighed carefully against the potential benefits to the woman and fetus when the advisability of participation is considered[28].

Although pregnancy is a time for caution when considering research trials, it also represents the only opportunity to study interventions aimed at treating pregnant women. For example, trials aimed at

determining appropriate tocolysis to prevent preterm birth or interventions to treat gestational diabetes can be conducted only during pregnancy. In addition, research during the process of labor and delivery is vital to improving care for women and their newborns. The fact that a pregnant woman is entering labor or in labor does not preclude her from consenting to participate in research[23]. A pregnant woman in labor may be able to undergo the appropriate informed consent process for research, similar to individuals with conditions that may have parallel connotations to labor, including life-threatening, emotionally distressing or emergency situation, e.g., appendicitis, cancer diagnosis and myocardial infarction[24].

Nonpregnancy-related interventions that may benefit a woman during pregnancy

A significant proportion of pregnant women undergo therapies aimed at managing nonobstetric medical conditions. Studies have estimated that more than 60% of pregnant women use at least one prescription medication during their pregnancies. Most of these medications have not specifically been studied during pregnancy. The unknown risk status of the vast majority of FDA-approved medications puts fetuses at risk[19]. Had these drugs been studied in pregnancy early in their use, data on risk may have provided an opportunity to better balance the risks and benefits of their use. Because pregnancies are increasingly occurring among older women and those with complex medical problems, the use of prescription medications by pregnant women is likewise increasing. Physicians who care for pregnant women with complex medical problems, and the pregnant women themselves, are faced with making health care decisions based on insufficient clinical evidence in an era when evidence-based medicine is standard practice[18, 19].

The challenge of caring for pregnant women on the basis of insufficient evidence is similar to treating children before reforms in responsible pediatric research. In 1994, the NIH publicly recognized a need for increased research in the pediatric population because of a significant gap in knowledge regarding safe and effective treatments[21]. Guidance required the default inclusion of children in clinical, social and behavioral research unless the investigator produced a cogent reason for their exclusion. As a result, current therapeutic information exists for some, though certainly not all, medications with respect to pediatric dosing, safety, and pharmacology[27, 28].

Broad exclusion of pregnant women from research trials actually may place fetuses at risk because of a resulting lack of applicable knowledge regarding how best to treat pregnant women with concomitant medical conditions. However, inclusion of a token number of pregnant women in a study would not provide sufficient meaningful information regarding the maternal and fetal effects of the intervention. Alternatively, requiring inclusion of an adequate number of pregnant women to meet power requirements for the primary outcome (or to exclude uncommon fetal morbidities) could raise prohibitive obstacles to research. Thus, thoughtful, responsible study design aimed at appropriate inclusion of pregnant women in research trials, when possible, while maintaining fetal safety as a key corollary consideration, is an important goal[25, 29].

Conclusion

All women, regardless of race, ethnicity, sexual orientation or socio-economic status, should be presumed eligible to participate in research studies. The potential for pregnancy should not automatically exclude a woman from participating in a study although the use of contraception may be required to participate. Including women in research studies is necessary for valid inferences about health and disease in women. The generalization of results from trials conducted among men may yield erroneous conclusions that fail to account for the biologic differences between men and women. Although many improvements have occurred since the time of systematic exclusion of women from research trials, more work needs to be completed concerning the design of research trials so that they do not inappropriately constrain the reproductive choices of study participants or unnecessarily exclude pregnant women. Importantly, researchers and funding organizations must recognize

the ways in which fertility, in the context of research trials, has been managed historically in a manner that is not evidence-based and is overly burdensome for female participants in research and that they make the necessary changes to remedy this situation.

Potential conflicts of interest

The author declare no conflict of interest.

References

1. International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition. Geneva. Council for International Organizations of Medical Sciences (CIOMS) 2016;69-73.
2. National Institutes of Health. NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research – amended, October 2001. Bethesda (MD): NIH; 2001. Available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Retrieved April 28, 2018.
3. National Institutes of Health. Revitalization Act of 1993 Public Law 103-43. Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies: Volume I.
4. National Institutes of Health. Monitoring adherence to the NIH policy on the inclusion of women and minorities as subjects in clinical research. Comprehensive report: tracking of clinical research as reported in fiscal year 2011 and fiscal year 2012. Bethesda (MD): NIH; 2013. Available at: http://orwh.od.nih.gov/research/inclusion/pdf/Inclusion-ComprehensiveReport-FY-2011-2012.pdf. Retrieved April 28, 2018.
5. Beauchamp TL, Childress JF. Principles of biomedical ethics. 7th ed. New York (NY): Oxford University Press; 2013.
6. Chen MS Jr, Lara PN, Dang JH, Paterniti DA, Kelly K. Twenty years' post-NIH Revitalization Act: enhancing minority participation in clinical trials (EMPaCT): laying the groundwork for improving minority clinical trial accrual: renewing the case for enhancing minority participation in cancer clinical trials. Cancer 2014;120 (suppl 7):1091–6.
7. Dickerson DL, Leeman RF, Mazure CM, O'Malley SS. The inclusion of women and minorities in smoking cessation clinical trials: a systematic review. Am J Addict 2009;18:21–8.
8. Geller SE, Koch A, Pellettieri B, Carnes M. Inclusion, analysis, and reporting of sex and race/ethnicity in clinical trials: have we made progress? J Womens Health (Larchmt) 2011;20:315–20.
9. Blehar MC, Spong C, Grady C, Goldkind SF, Sahin L, Clayton JA. Enrolling pregnant women: issues in clinical research. Womens Health Issues 2013;23:39–45.
10. National Bioethics Advisory Commission. Ethical and policy issues in research involving human participants. Bethesda (MD): NBAC; 2001. Available at: https://bioethicsarchive.georgetown.edu/nbac/human/overvol1.pdf. Retrieved April 28, 2015.
11. Anderson JR, Schonfeld TL, Kelso TK, Prentice ED. Women in early phase trials: an IRB's deliberations. IRB 2003;25:7–11.
12. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease [published erratum appears in Toxicol Sci 2012;125:613]. Toxicol Sci 2011;122:1–6.
13. Teo SK, Harden JL, Burke AB, Noormohamed FH, Youle M, Johnson MA, et al. Thalidomide is distributed into human semen after oral dosing. Drug Metab Dispos 2001;29:1355–7.
14. Geiger CJ, Fahrenbach DM, Healey FJ. Bendectin in the treatment of nausea and vomiting in pregnancy. Obstet Gynecol 1959;14:688–90.
15. Mitchell AA, Rosenberg L, Shapiro S, Slone D. Birth defects related to bendectin use in pregnancy. I. Oral clefts and cardiac defects. JAMA 1981;245:2311–4.
16. Zierler S, Rothman KJ. Congenital heart disease in relation to maternal use of bendectin and other drugs in early pregnancy. N Engl J Med 1985;313:347–52.
17. Holmes LB. Teratogen update: bendectin. Teratology 1983;27:277–81.
18. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology 1994;50:27–37.
19. Gee RE, Wood SF, Schubert KG. Women's health, pregnancy, and the U.S. Food and Drug Administration. Obstet Gynecol 2014;123:161–5.
20. Daw JR, Mintzes B, Law MR, Hanley GE, Morgan SG. Prescription drug use in pregnancy: a retrospective, population-based study in British Columbia, Canada (2001-2006). Clin Ther 2012;34:239–49.
21. National Institutes of Health. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Bethesda (MD): NIH; 1998. Available at: http://grants.nih.gov/grants/guide/notice-files/not98-024.html. Retrieved April 28, 2018.
22. Shaddy RE, Denne SC. Clinical report - guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. Committee on Drugs and Committee on Pediatric Research. Pediatrics 2010;125:850–60.
23. Lyerly AD, Namey EE, Gray B, Swamy G, Faden RR. Women's views about participating in research while pregnant. IRB 2012;34:1–8.
24. Maternal-fetal intervention and fetal care centers.

Committee Opinion No. 501. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:405–10.
25. Informed consent. ACOG Committee Opinion No. 439. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;114:401–8.
26. Lyerly AD, Mitchell LM, Armstrong EM, Harris LH, Kukla R, Kuppermann M, et al. Risk and the pregnant body. Hastings Cent Rep 2009;39:34–42.
27. Neill KM. Research subject advocate: a new protector of research participants. Account Res 2003;10:159–74.
28. Silber TJ. Human gene therapy, consent, and the realities of clinical research: is it time for a research subject advocate? Hum Gene Ther 2008;19:11–4.
29. National Human Research Protections Advisory Committee. Comment letter to HHS on 45 CFR 46 Subpart B—September 2001. Washington, DC: NHRPAC; 2001. Available at: http://www.hhs.gov/ohrp/archive/nhrpac/documents/oct01c.pdfc/documents/oct01c.pdf. Retrieved April 28, 2018.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 149-157

OBSTETRICS

Accuracy of Capillary Glucose Testing in Gestational Diabetes Screening

Arisa Kongcharoensukying, M.D.,*,
Boonlert Viriyapak, M.D.,*,
Dittakarn Boriboonhirunsarn, M.D., M.P.H., Ph.D.,*.

** Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*

ABSTRACT

Objectives: To assess the accuracy of capillary whole blood glucose compared to conventional venous plasma glucose testing for 50-g GCT in gestational diabetes mellitus (GDM) screening.

Materials and Methods: A total of 180 women at-risk for GDM were randomly selected and enrolled and a 50-g GCT was offered as a screening test. At 1 hour after glucose loading, a capillary glucose testing was performed by well-trained nurses using a Nova Biomedical StatStrip®. Within 5 minutes after capillary glucose test, venipuncture was then performed by certified technicians and venous blood was sent to a certified central laboratory to determine plasma glucose value. Results from POCT glucose testing were compared with venous plasma glucose (gold standard) to evaluate for its accuracy. Women with venous plasma glucose ≥ 140 mg/dL were offered 100-g OGTT for GDM diagnosis according to current guideline.

Results: Mean age was 33.1 years and 53.9% were nulliparous. Common GDM risks were age ≥ 30 years (87.8%), family history of DM (32.2%), and BMI ≥ 25 kg/m^2 (25%). Mean gestational age at screening was 14.4 weeks. Mean venous plasma glucose was 131.6 ± 34.9 mg/dL and mean POCT glucose was 149.3 ± 27.7 mg/dL. Mean difference was 17.7 ± 19.4 mg/dL, corresponding to 16.8 ± 18.3%. POCT results were significantly correlated with venous plasma glucose (correlation coefficient 0.832, $p < 0.001$). GDM was diagnosed in 16 women (8.9%). At 140 mg/dL cut off, abnormal GCT was found in 37% by venous plasma glucose and 61% by POCT glucose results. Using 140 mg/dL cut off, POCT glucose has 97.1% sensitivity and 73.9% accuracy. At 165 mg/dL cut off, POCT glucose has 98.2% specificity and 82.8% accuracy.

Conclusion: POCT capillary glucose testing could be considered as an alternative to conventional venous glucose testing for 50-g GCT for GDM screening using 140 and 165 mg/dL cut off values.

Keywords: gestational diabetes, 50-g glucose challenge test, venous plasma glucose, capillary glucose, accuracy.

Correspondence to: *Dittakarn Boriboonhirunsarn, M.D., M.P.H., Ph.D., Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*
Telephone: (662) 419-7000, Ext 4637, FAX: (662) 418-2662, Email address: dittakarn.bor@mahidol.ac.th, ORCID ID: orcid.org/0000-0002-5901-5923

ความแม่นยำของการใช้การตรวจน้ำตาลจากปลายนิ้ว ในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์

อริสา คงเจริญสุขยิ่ง, บุญเลิศ วิริยะภาค, ดิฐกานต์ บริบูรณ์หิรัญสาร

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาความแม่นยำของการใช้การตรวจน้ำตาลจากปลายนิ้ว ณ จุดดูแลผู้ป่วย ในการตรวจคัดกรองภาวะเบาหวานขณะตั้งครรภ์*

วัสดุและวิธีการ: *ทำการศึกษาโดยสุ่มเลือกสตรีตั้งครรภ์ที่มีความเสี่ยงต่อภาวะเบาหวานขณะตั้งครรภ์ จำนวน 180 ราย ที่ได้รับการตรวจคัดกรองด้วยวิธี 50-g glucose challenge test หลังจากกินน้ำตาล 1 ชั่วโมง ทำการเจาะเลือดจากปลายนิ้วและตรวจด้วยเครื่องตรวจน้ำตาลในเลือด ณ จุดดูแลผู้ป่วย (Nova Biomedical StatStrip®) โดยพยาบาลผู้ชำนาญ จากนั้นภายใน 5 นาที ทำการเจาะเลือดจากหลอดเลือดดำโดยเจ้าหน้าที่ห้องปฏิบัติการ และส่งตรวจโดยวิธีมาตรฐานที่ห้องปฏิบัติการกลาง เพื่อตรวจระดับน้ำตาล ทำการเปรียบเทียบผลน้ำตาลจากการตรวจทั้ง 2 วิธี โดยใช้ค่าน้ำตาลที่ได้จากการเจาะหลอดเลือดดำเป็นมาตรฐาน เพื่อประเมินความถูกต้องแม่นยำ สตรีตั้งครรภ์ที่ผลน้ำตาลจากการเจาะหลอดเลือดดำ ≥ 140 มก/ดล จะได้รับการตรวจวินิจฉัยต่อไปตามแนวทางการดูแลมาตรฐาน*

ผลการศึกษา: *สตรีตั้งครรภ์มีอายุเฉลี่ย 33.1 ปี เป็นครรภ์แรก 53.9 เปอร์เซ็นต์ ตวามเสี่ยงต่อภาวะเบาหวานระหว่างตั้งครรภ์ที่พบบ่อย ได้แก่ อายุ ≥ 30 ปี (ร้อยละ 87.8), ประวัติเบาหวานในครอบครัว (ร้อยละ 32.2), และค่าดัชนีมวลกาย ≥ 25 กก/ม^2 (ร้อยละ 25) อายุครรภ์เฉลี่ยที่ทำการตรวจคัดกรอง คือ 14.4 สัปดาห์ ค่าเฉลี่ยของระดับน้ำตาลจากการเจาะหลอดเลือดดำเท่ากับ 131.6 ± 34.9 มก./ดล. และค่าเฉลี่ยของระดับน้ำตาลจากการเจาะเลือดปลายนิ้ว เท่ากับ 149.3 ± 27.7 มก./ดล. ค่าเฉลี่ยความแตกต่างเท่ากับ 17.7 ± 19.4 มก./ดล. หรือร้อยละ 16.8 ± 18.3 ผลการตรวจจากการเจาะเลือดปลายนิ้ว สัมพันธ์กับผลการตรวจจากหลอดเลือดดำอย่างมีนัยสำคัญทางสถิติ (correlation coefficient 0.832, $p < 0.001$) ตรวจพบภาวะเบาหวานระหว่างตั้งครรภ์ 16 ราย ร้อยละ 8.9 ตรวจพบความผิดปกติของค่า GCT ที่จุดตัด 140 มก./ดล. 37 เปอร์เซ็นต์ จากการเจาะหลอดเลือดดำ และร้อยละ 61 จากการเจาะเลือดปลายนิ้ว พบว่าการใช้ค่าจุดตัดที่ 140 มก./ดล. การเจาะเลือดปลายนิ้วมีค่าความไว ร้อยละ 97.1 และมีค่าความแม่นยำร้อยละ 73.9 และที่ค่าจุดตัดที่ 165 มก./ดล. การเจาะเลือดปลายนิ้วมีค่าความจำเพาะร้อยละ 98.2 และมีค่าความแม่นยำร้อยละ 82.8*

สรุป: *การตรวจคัดกรองภาวะเบาหวานระหว่างตั้งครรภ์ด้วยเครื่องตรวจน้ำตาลจากปลายนิ้ว ณ จุดดูแลผู้ป่วย เป็นทางเลือกที่ดีในการตรวจแทนการเจาะเลือดจากหลอดเลือดดำ โดยมีค่าจุดตัดในการตรวจคัดกรองที่เหมาะสมคือ 140 และ 165 มก./ดล.*

คำสำคัญ: *ภาวะเบาหวานระหว่างตั้งครรภ์, 50-g glucose challenge test, ระดับน้ำตาลจากปลายนิ้ว, ระดับน้ำตาลจากหลอดเลือดดำ, ความแม่นยำ*

Introduction

Gestational diabetes mellitus (GDM), a condition in which carbohydrate intolerance develops during pregnancy, is one of the most common medical complications of pregnancy[1-3]. GDM is associated with a higher incidence of maternal morbidity including cesarean deliveries, shoulder dystocia, birth trauma, hypertensive disorders of pregnancy, and subsequent development of Type-2 DM. Perinatal and neonatal morbidities also increase, including macrosomia, birth injury, hypoglycemia, polycythemia, hyperbilirubinemia, and increased risks for obesity and diabetes later in life[1-3].

Although no global consensus has yet been established for GDM screening and diagnostic strategy, a 2-step approach is currently recommended by the American College of Obstetricians and Gynecologists (ACOG) and the American Diabetes Association (ADA)[1, 2]. A 50-g glucose challenge test (GCT) is used as a screening test, and individuals meeting or exceeding the screening threshold then undergo a 100-g oral glucose tolerance test (OGTT) for GDM diagnosis. Screening is generally performed at 24-28 weeks of gestation, but early screening is suggested in high-risk women. Repeat screening is recommended at 24-28 weeks of gestation if the result of early testing is negative.

All the tests are analyzed from venous plasma glucose, based on glucose oxidase–peroxidase method, as a standard for interpretation of the results. However, there are some drawbacks to be considered including the need of venipuncture, cost, and long results turnaround time. Point-of-care-test (POCT) for capillary glucose, using a certified glucose meter, has been extensively used in diabetes management for many decades. However, their use has not been advocated for GDM screening and diagnosis due to possible errors in measurement. As the reliability of glucose meter has been improved, several studies have evaluated the use of portable meters in screening for GDM. The use of various glucose meters for GDM screening with acceptable accuracy and reliability have been reported[4-8]. The use of POCT glucose for GDM screening has been reported to be cost-effective that standard laboratory studies can be avoided in 90% of patients[9]. A recent study reported that the use of POCT glucose has considerable potential for GDM screening and diagnosis using adjusted cutoff, particularly in healthcare settings with limited resources[5, 10-13].

In Siriraj Hospital, GDM screening by 50-g GCT is used and the results are analyzed by standard laboratory technic. As the hospital is a university-based tertiary care hospital, the results turnaround time can take up to 1 to 2 hours. As a consequence, many women are frequently informed about the results in their next visit. This also cause a delay in further OGTT for GDM diagnosis as well as initiation of treatment. Since 2008, POCT for capillary glucose, using certified glucose meter, has been used widely for improving patient care in Siriraj Hospital. However, its use in GDM screening is still not endorsed.

Due to some drawbacks and limitations of standard technic for GDM screening, POCT could be a potential alternative for 50-g GCT. Besides cost savings, the immediate results obtained by POCT measurement would allow for prompt identification of abnormal screening results and prompt scheduling for further evaluation of glucose intolerance during the pregnancy. However, data on the use of POCT for GDM screening is still limited in Thailand. Previously, there was only one study in southern Thailand and the results showed good correlation between capillary and venous plasma glucose and at 140 mg/dL cut-off, glucose meter has a sensitivity and specificity of 93.8% and 83.6% for detecting abnormal screening test[14]. However, the device for capillary glucose measurement has now been improved to meet the stricter International Organization for Standardization (ISO) standard and population and screening strategy are also differ between settings that the results might not be applied to our population.

Therefore, the objectives of this study were to

assess the accuracy of the POCT of capillary whole blood glucose compared to conventional venous plasma glucose testing for 50-g GCT in GDM screening and to determine appropriate cutoff values for POCT results to be applied for clinical use.

Materials and Methods

After approval of Siriraj Institutional Review Board, a prospective study was conducted at antenatal clinic of Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital. During July and December 2016, a total of 180 pregnant women who were at risk for gestational diabetes were enrolled. Women with pre-gestational diabetes and those who did not agree to participate were excluded.

According to the institutional clinical practice guideline at our center[15], GDM screening and diagnosis is offered to all at-risk women. Risk factors for GDM include age ≥ 30 years, pre-pregnancy body mass index (BMI) ≥ 25 kg/m^2, family history of diabetes, presence of hypertension, previous GDM, and history of fetal macrosomia, stillbirth, or fetal anomaly. A 50-g GCT with a cut-off value of ≥ 140 mg/dL is used for GDM screening. For patients who meet or exceed the cut-off value of 140 mg/dL, a 100-g OGTT is used to diagnose the GDM using the criteria of Carpenter and Coustan. These procedures are offered during the patient's first visit, and they are then repeated at 24-28 weeks of gestation if the first screening result was normal. All GDM women receive dietary therapy, and insulin treatment is added as needed.

Pregnant women at any gestational age who were indicated for 50-g GCT were randomly selected to enroll in this study. After informed consent, all participants were offered GDM screening with 50-g GCT. At 1 hour after glucose load, venous and capillary blood were collected to determine glucose level. Capillary blood glucose determination was performed by well-trained nurses by POCT using StatStrip® glucose meter, which is a certified glucose meter currently used at Siriraj Hospital. The test principle used is electrochemical biosensor technology using glucose oxidase. The strip uses the enzyme glucose oxidase to produce an electrical current that will stimulate a chemical reaction. This reaction is measured by the device and displayed as a bloodglucose result. The glucose meter was calibrated and validated following the manufacturer's guidelines. Within 5 minutes after capillary glucose measurement, the patients were sent for venipuncture by certified hospital technicians to determine venous plasma glucose levels. Venous plasma glucose was measured by the glucose oxidase–peroxidase method autoanalyzer from the ISO-certified central laboratory. Interpretation of the results and further GDM diagnosis and management were provided according to the results of venous plasma glucose level as appropriate.

Sample size calculation was based on estimated sensitivity and specificity of POCT glucose at 87.5% and 50% from a pilot study, respectively, and prevalence of abnormal GCT of 40%. At 95% significance level and 80% a sample size of at least 162 cases were required with 10% acceptable error.

Descriptive statistics were used to describe various baseline characteristics and 50-g GCT results, using number, percentage, mean, and standard deviation, as appropriate. Differences between POCT and venous plasma glucose were evaluated in both absolute and percentage differences. Pearson correlation coefficient was used to assess correlation between the 2 glucose results. Sensitivity, specificity, positive and negative predictive values (PPV and NPV), and accuracy of POCT glucose for determining abnormal 50-g GCT were estimated, using venous plasma glucose level as a gold standard. A p value of < 0.05 was considered statistical significance.

Results

A total of 180 pregnant women who were at risk for GDM were enrolled during August and November 2016. Table 1 shows baseline characteristics of the participants. Mean age was

33.1 ± 4.3 years, and majority of them were nulliparous (53.9%). Mean BMI 22.8 ± 4.3 kg/m^2 and 25% had BMI ≥ 25 kg/m^2. Common GDM risks were age ≥ 30 years (87.8%), family history of diabetes mellitus (32.2%), and overweight (23.9%).

Table 2 shows the characteristics of GDM screening and results. Mean gestational age at screening was 14.4 ± 8.9 week, mean venous plasma glucose was 131.6 ± 34.9 mg/dL and mean POCT glucose was 149.3 ± 27.7 mg/dL. Glucose level from POCT was higher than venous plasma with the mean of 17.7 ± 19.4 mg/dL, corresponding to 16.8 ± 18.3%. Abnormal GCT (≥ 140 mg/dL) from venous plasma glucose results were 37%, while it was 61% from POCT results. GDM was diagnosed in 16 cases (8.9%) and all had POCT glucose of ≥ 140 mg/dL. Among them, 1 had POCT glucose 140-164 mg/dL and 15 had POCT glucose ≥ 165 mg/dL.

Table 1. Baseline characteristics of the patients (N=180).

Characteristic	Mean ± SD
Age (years)	33.1 ± 4.3
BMI (kg/m^2)	22.8 ± 4.3
	N (%)
Nulliparous	97 (53.9)
BMI category	
Normal (BMI 18-24.9 kg/m^2)	114 (63.3)
Underweight (BMI <18 kg/m^2)	21 (11.7)
Overweight (BMI ≥ 25 kg/m^2)	45 (25)
Risk factors for GDM	
Age ≥ 30	158 (87.8%)
Family history of diabetes mellitus	58 (32.2%)
BMI ≥ 25 kg/m^2	45 (25%)
History of GDM	7 (3.9%)
Previous stillbirth	1 (0.6%)

Table 2. Capillary and venous plasma glucose results of 50-g GCT for GDM screening (N=180).

GDM screening results	Mean ± SD
GA at 50-g GCT (weeks)	14.4 ± 8.9
Venous plasma glucose (mg/dL)	131.6 ± 34.9
POCT glucose (mg/dL)	149.3 ± 27.7
Difference of glucose result (mg/dL)	17.7 ± 19.4
Percentage difference (%)	16.8 ± 18.3
	N (%)
Venous plasma glucose ≥ 140 mg/dL	68 (37%)
POCT glucose ≥ 140 mg/dL	111 (61%)

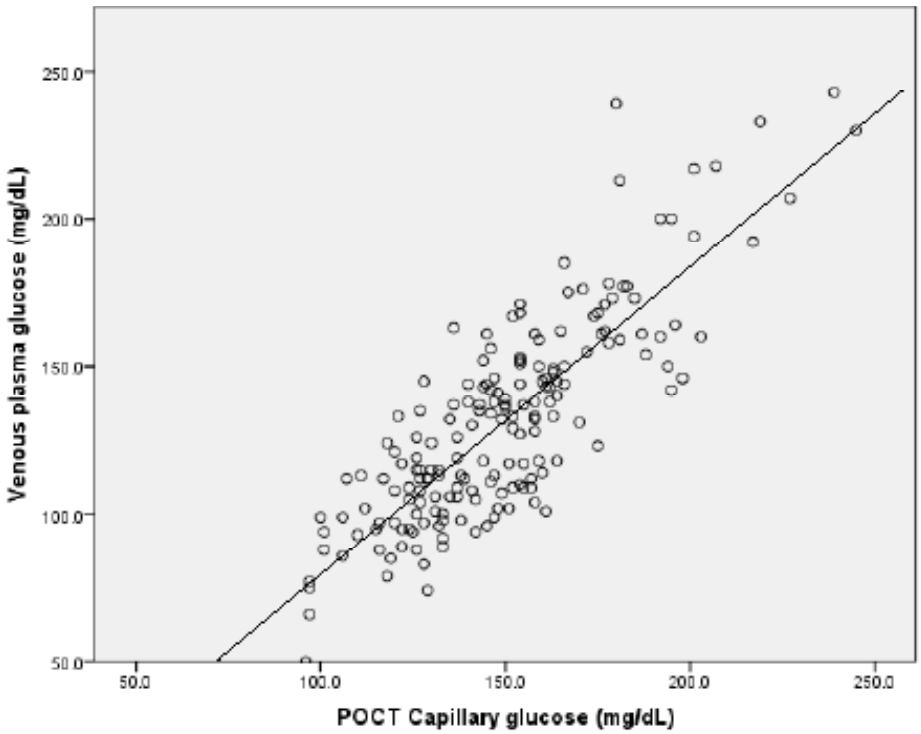

Fig. 1. Correlation between POCT and venous plasma glucose results (correlation coefficient 0.832, $p < 0.001$).

Table 3. Comparison between venous plasma and POCT glucose results of 50-g GCT.

		Venous plasma glucose		Total
		< 140 mg/dL	**≥ 140 mg/dL**	
POCT glucose	< 140 mg/dL	67	2*	69
	140 -164 mg/dL	43	27	70
	≥ 165 mg/dL	2	39	41
Total		**112**	**68**	**180**

* The 2 cases had normal 100-g OGTT results

Correlation between POCT and venous plasma glucose results are demonstrated in a scatter plot (Fig. 1). A significant correlation was observed between the 2 tests with Pearson correlation coefficient of 0.832, $p < 0.001$. Intraclass correlation coefficient was 0.811, $p < 0.001$.

Comparison between venous plasma and POCT glucose results of 50-g GCT is demonstrated in Table 3. Various cutoff values of capillary glucose results were evaluated that the lower cutoff should have high sensitivity and NPV that would miss only a few cases of abnormal GCT and the upper should have high specificity and PPV that would include only a few cases of normal GCT that need unnecessary OGTT. In addition, the proportion of pregnant women who still needed venipuncture for venous plasma glucose level were also considered. After such considerations, cutoff values of 140 and 165 mg/dL

was selected.

At 140 mg/dL cutoff for determining of abnormal GCT, POCT has sensitivity of 97.1% (95% CI 89.8-99.6), specificity of 59.8% (95% CI 50.1-69.0), PPV of 59.5% (95% CI 49.7-68.7), NPV of 97.1% (95% CI 89.8-99.6), and accuracy of 73.9% (95% CI 66.8-80.1). On the other hand, at 165 mg/dL cutoff, POCT has sensitivity of 57.4% (95% CI 44.8-69.3), specificity of 98.2% (95% CI 93.7-99.8), PPV of 95.1% (95% CI 83.5-99.4), NPV of 79.1% (95% CI 71.4-85.6), and accuracy of 82.8% (95% CI 76.5-88.0).

There were 2 cases who would have been missed for abnormal 50-g GCT (POCT < 140 mg/dL but venous plasma glucose ≥ 140 mg/dL) were further received 100-g OGTT and the results were normal. There were also another 2 cases that unnecessary 100-g OGTT would have been performed (POCT ≥ 165 mg/dL but venous plasma glucose < 140 mg/dL) if such cutoff values were used. It can be noted that, if POCT was used instead of venous plasma glucose with the cutoff at 140 and 165 mg/dL, 69 women (38.3%) could be assumed that they have normal GCT and 41 women (22.8%) will need 100-g OGTT to confirm diagnosis. Only 70 women (38.9%) would need confirmation with venous plasma glucose to determine GCT abnormalities.

Discussion

The results of this study showed that glucose measurement by POCT using a glucose meter correlated well with the standard laboratory technic for 50-g GCT (correlation coefficient 0.832, p<0.001) and POCT results was approximately 17.7 mg/dL (16.8%) higher than venous plasma glucose. The results were similar to previous studies that reported good correlation of the results between the 2 technics with correlation coefficients between 0.8 to 0.93[11, 14, 16] and that the results from POCT were higher than venous plasma values[8, 11, 14].

Although the POCT capillary blood glucose determination was accurate and correlate well with standard laboratory technic, the direct substitution of plasma glucose values with capillary glucose values in screening for or diagnosing GDM is still not recommended[16]. However, it is recommended that specific cutoff values for each glucose meter be established for each facility[9]. For the use of POCT in GDM screening, various thresholds have been reported. A threshold of 163 mg/dL has also been reported from earlier study with sensitivity and specificity of 85.7% and 86.8%[17]. Another study reported that cutoff of POCT at 155 mg/dL may be more appropriate for GDM screening, considering the 10-15% higher capillary glucose level, with sensitivity and specificity of 81% and 74%[8]. A more recent study in Thailand reported that the threshold of 140 mg/dL yielded sensitivity and specificity of 93.8% and 83.6%[14].

The results of this study showed that, at 140 mg/dL cut-off, the use of POCT would almost double the abnormal screening results and the need for 100-g OGTT, i.e., from 37% by venous plasma glucose to 61% by POCT. Although the sensitivity was 97.1%, the specificity was only 59.8%, which correspond to 40.2% false positive rate. Therefore, another cut-off value at 165 mg/dL was evaluated and the results showed that specificity increased to 98.2%. The use of both cut-off values at 140 and 165 mg/dL would be more appropriate that they would give high sensitivity at 140 mg/dL to "rule out" and high specificity at 165 mg/dL to "rule in" women with abnormal 50-g GCT.

If POCT is used in clinical practice, based on the results of this study, 38.3% of the women can be reassured of normal test results (POCT < 140 mg/dL), and another 22.8% can be immediately scheduled for 100-g OGTT (POCT ≥ 165 mg/dL). Venipuncture for plasma glucose testing can also be avoided in these women. Only 38.9% will require standard venous plasma glucose testing to confirm the results. A previous study also reported that, by using POCT for GDM screening, as many as 90% of patients will not require laboratory studies[9]. This will result in significant cost savings and, in addition, the immediate results obtained by POCT will allow for prompt identification of an abnormal screen and prompt scheduling for further evaluation of glucose intolerance during the pregnancy. Some studies have suggested that the use of POCT

capillary glucose for GDM screening might be more appropriate in resource-constraint settings, such as where standard laboratory technic is not readily available or in a community-based practice[5, 12, 13].

Differences in the results between studies might partly be due to differences in GDM risks in each population, screening and diagnostic strategies and criteria used, and types of glucose meters used. However, all the results were in the same direction that POCT results were accurate and can be applied in clinical practice as a substitution for standard venous plasma glucose determination for GDM screening.

Some limitations of this study should be mentioned. Time lag between POCT and venipuncture for plasma glucose testing could possibly deviate the results. However, in this study, venipuctures were no later than 10 minutes after POCT that the delay should not seriously affect the results. Moreover, generalization of the results to other clinical settings might be limited due to differences in baseline GDM risks and screening and diagnostic strategies and criteria used. Different types of glucose meter for POCT might produce different results that the threshold to be used for GDM screening should be evaluated and applied in each setting. Technical errors from the use of glucose meter in this study should be minimal since the tests were performed by well-trained personnel who are familiar with the equipment.

Given many advantages of POCT for glucose determination, such as lower cost, simplicity, better patient acceptance, and immediate availability of the result, capillary blood glucose testing should be considered as a good alternative for GDM screening in routine clinical practice, especially in settings with limited resources.

Conclusion

Glucose measurement by POCT correlated well with the standard laboratory technic for 50-g GCT for GDM screening (correlation coefficient 0.832, $p < 0.001$). The POCT results was approximately 17.7 mg/dL (16.8%) higher than venous plasma glucose. The cut-off values at 140 and 165 mg/dL provided sensitivity of 97.1% and 98.2%, respectively. If POCT is used, venipuncture for plasma glucose can be avoided in approximately 60% of pregnant women.

Acknowledgement

The authors gratefully acknowledge Miss Maria Asad-dehghan for assistance with data collection procedure.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. American College of Obstetricians and Gynecologists. Committee on Practice Bulletins-Obstetrics. Practice Bulletin No. 180: Gestational diabetes mellitus. Obstet Gynecol 2017;130:e17-31.
2. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2017;40:S11-24.
3. Hod M, Kapur A, Sacks DA, Hadar E, Agarwal M, Di Renzo GC, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on gestational diabetes mellitus: A pragmatic guide for diagnosis, management, and care. Int J Gynaecol Obstet 2015;131:S173-211.
4. Buhling KJ, Henrich W, Kjos SL, Siebert G, Starr E, Dreweck C, et al. Comparison of point-of-care-testing glucose meters with standard laboratory measurement of the 50g-glucose-challenge test (GCT) during pregnancy. Clin Biochem 2003;36:333-7.
5. Bhavadharini B, Mahalakshmi MM, Maheswari K, Kalaiyarasi G, Anjana RM, Deepa M, et al. Use of capillary blood glucose for screening for gestational diabetes mellitus in resource-constrained settings. Acta Diabetol 2016;53:91-7.
6. Dhatt GS, Agarwal MM, Othman Y, Nair SC. Performance of the Roche Accu-Chek active glucose meter to screen for gestational diabetes mellitus using fasting capillary blood. Diabetes Technol Ther 2011;13:1229-33.
7. Carr SR, Slocum J, Tefft L, Haydon B, Carpenter M. Precision of office-based blood glucose meters in screening for gestational diabetes. Am J Obstet Gynecol 1995;173:1267-72.
8. Murphy NJ, Meyer BA, O'Kell RT, Hogard ME. Screening for gestational diabetes mellitus with a reflectance photometer: accuracy and precision of the single-operator model. Obstet Gynecol 1994;83:1038-42.
9. Teplick FB, Lindenbaum CR, Cohen AW. Cost-effective

approach to office screening for gestational diabetes. J Perinatol 1990;10:301-3.
10. Daly N, Carroll C, Flynn I, Harley R, Maguire PJ, Turner MJ. Evaluation of point-of-care maternal glucose measurements for the diagnosis of gestational diabetes mellitus. BJOG 2017;124:1746-52.
11. Marley JV, Davis S, Coleman K, Hayhow BD, Brennan G, Mein JK, et al. Point-of-care testing of capillary glucose in the exclusion and diagnosis of diabetes in remote Australia. Med J Aust 2007;186:500-3.
12. Balaji V, Balaji MS, Paneerselvam A, Thiyagarajah A, Seshiah V. Point of care for gestational diabetes mellitus--a community-based study. J Indian Med Assoc 2012; 110:314-6.
13. Balaji V, Madhuri BS, Paneerselvam A, Arthi T, Seshiah V. Comparison of venous plasma glucose and capillary whole blood glucose in the diagnosis of gestational diabetes mellitus: a community-based study. Diabetes Technol Ther 2012;14:131-4.
14. Srimaekarat T. Capillary blood glucose screening (Accu-Chek Advantage) for gestational diabetes. J Med Assoc Thai 2009;92:1268-72.
15. Sunsaneevithayakul P, Boriboohirunsarn D, Sutanthavibul A, Ruangvutilert P, Kanokpongsakdi S, Singkiratana D, et al. Risk factor-based selective screening program for gestational diabetes mellitus in Siriraj Hospital: result from clinical practice guideline. J Med Assoc Thai 2003; 86:708-14.
16. Dacus JV, Schulz K, Sibai BM, Gonzalez-Ruiz A. Comparison of capillary and plasma glucose values in screening and oral glucose tolerance testing in pregnancy. J Reprod Med 1990;35:1150-2.
17. Yoo T, Chao J. Screening for gestational diabetes mellitus. Use and accuracy of capillary blood glucose measured with a reflectance meter. J Fam Pract 1989; 29:41-4.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 158-165

OBSTETRICS

Efficacy of Music Therapy on Immediate Postpartum Episiotomy Pain: A randomized controlled trial

Ravita Chaichanalap, M.D.*,
Wipada Laosooksathit, M.D.*,
Kittipong Kongsomboon, M.D., MBA, PhD**,
Tharangrut Hanprasertpong, M.D.*..

** Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot university, Ongkharak, Nakornnayok 26120, Thailand*

*** Department of preventive and social medicine, Faculty of Medicine, Srinakharinwirot university, Ongkharak, Nakornnayok 26120, Thailand*

ABSTRACT

Objectives: To evaluate the effectiveness of music therapy in alleviating immediate postpartum episiotomy wound pain.

Materials and Methods: A randomized controlled trial was conducted to evaluate the efficacy of music therapy in alleviating immediate pain from an episiotomy wound. Uncomplicated singleton vaginal delivery women with the second degree or less episiotomy wound at Delivery and Postpartum Inpatient Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Thailand were enrolled into the study. Visual analog scale (VAS) scoring was used for comparing pain levels.

Results: One hundred postpartum women were enrolled in our study. Baseline characteristics such as age, degree of episiotomy wound tear were similar between both groups. The median pain VAS score was statistically significantly lower in the music group than in the control group at the end of the 2nd hour after finish of episiotomy wound repairing process [24.0 millimeters (8.3-41.5) and 36.5 millimeters (20.0-53.3), $p < 0.001$]. The median pain VAS score was statistically significantly lower in the music group than in the control group at the end of 6th hour after finish of episiotomy wound repairing process [12.0 millimeters (3.0-21.0) and 22.0 millimeters (15.0-38.0), $p < 0.001$]

Conclusion: Music therapy is effective for reducing the perceived immediate postpartum pain of an episiotomy wound.

Keywords: episiotomy pain, music therapy, singleton pregnancy.

Correspondence to: *Tharangrut Hanprasertpong, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, Srinakharinwirot University, Ongkharak, Nakhon Nayok 26120, Thailand*
Telephone: 66-37095085-6 ext 10803, Email: tharangrut@hotmail.com, tharangrut@gmail.com

ประสิทธิภาพของดนตรีบำบัดในการบรรเทาความรู้สึกเจ็บปวดจากแผลฝีเย็บช่วงหลังคลอดทันที: การศึกษาแบบสุ่มและมีกลุ่มควบคุม

รวิตา ชัยชนะลาภ, วิภาดา เหล่าสุขสถิตย์, กิตติพงษ์ คงสมบูรณ์, ธารางรัตน์ หาญประเสริฐพงษ์

บทคัดย่อ

***วัตถุประสงค์**: เพื่อศึกษาประสิทธิภาพของดนตรีบำบัดต่อการบรรเทาความรู้สึกเจ็บปวดจากแผลฝีเย็บช่วงหลังคลอดทันที*

***วัสดุและวิธีการ**: การศึกษาแบบสุ่มและมีกลุ่มควบคุมเพื่อประเมินประสิทธิภาพของดนตรีบำบัดต่อการบรรเทาความรู้สึกเจ็บปวดจากแผลฝีเย็บช่วงหลังคลอดทันที หญิงหลังคลอดทางช่องคลอดซึ่งได้รับการตัดฝีเย็บระดับ 2 หรือน้อยกว่า โดยไม่มีอาการแทรกซ้อนของการคลอด ที่ห้องคลอดและหอผู้ป่วยในหลังคลอดของภาควิชาสูติศาสตร์นรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ ซึ่งได้รับคำเชิญให้ร่วมในการศึกษานี้ โดยใช้มาตรวัดความเจ็บปวดด้วยสายตาเปรียบเทียบระดับความปวดระหว่างกลุ่มศึกษาและกลุ่มควบคุม*

***ผลการศึกษา**: หญิงหลังคลอด 100 คน ได้รับเชิญให้เข้าร่วมในการศึกษานี้ ลักษณะพื้นฐานของผู้เข้าร่วมการศึกษาเช่น อายุ ระดับความรุนแรงของการฉีกขาดแผลฝีเย็บเหมือนกันในทั้งสองกลุ่มผู้เข้าร่วมการศึกษา ค่ามัธยฐานของระดับความเจ็บปวดวัดโดยใช้มาตรวัดความเจ็บปวดด้วยสายตา ณ. เวลา 2 ชั่วโมงหลังสิ้นสุดการเย็บแผลฝีเย็บของกลุ่มศึกษาต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ [24.0 มิลลิเมตร (8.3-41.5) และ 36.5 มิลลิเมตร (20.0-53.3) ตามลำดับ, ค่า $p < 0.001$] ค่ามัธยฐานของระดับความเจ็บปวดวัดโดยใช้มาตรวัดความเจ็บปวดด้วยสายตา ณ. เวลา 6 ชั่วโมงหลังสิ้นสุดการเย็บแผลฝีเย็บของกลุ่มศึกษาต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ [12.0 มิลลิเมตร (3.0-21.0) and 22.0 มิลลิเมตร (15.0-38.0) ตามลำดับ, ค่า $p < 0.001$]*

***สรุป**: ดนตรีบำบัดมีประสิทธิภาพในการบรรเทาความรู้สึกเจ็บปวดจากแผลฝีเย็บช่วงหลังคลอดทันที*

***คำสำคัญ**: เจ็บปวดแผลฝีเย็บ, ดนตรีบำบัด, หญิงตั้งครรภ์เดี่ยว*

Introduction

Episiotomy is a common obstetric procedure which is often performed during a vaginal delivery in Thailand. Benefits of the episiotomy include decreasing third-degree vaginal tearing, prevention of pelvic floor muscle relaxation, and they are easier to repair and heal better than spontaneous lacerations[1]. However, pain and edema in the episiotomy area following the birth can cause discomfort and interfere with ambulation, breastfeeding, slower resumption of normal sexual function and defecation and urination functions[2]. Many modalities have been introduced for reducing episiotomy pain, such as administration of local anesthetics (lidocaine gel, spray or injection, oral or intravenous pain killer)[3-4]. However all of these methods involve adverse effects such as rash, gastrointestinal tract disturbance or allergic reactions.

Music therapy is an alternative medicine which has been found to be effective in reducing in many medical situation, including laparoscopic cholecystectomy and open heart surgery[5-6]. Music therapy functions to control pain via the pain gate control theory, which states that pain fibers from injured tissue activate the pain gate at the spinal gating system of the spinal cord. Music closes the pain gate and therefore inhibits pain signals from being transmitted from the wound site to the brain. Furthermore, it is hypothesized that music therapy activates the anterior pituitary gland to release endorphins which relieve pain. Relaxation music without lyrics included synthesizer, harp, piano, orchestra and jazz with slow beat 60-80 beats per minute were used post-operative for 60 minutes and pain was reduced approximately 30 percent[7-9]. However, to date there have no study which have evaluated the effectiveness of music therapy in alleviating the pain arising from an episiotomy in immediate postpartum period. Thus, we conducted this study which aimed to analyze the efficacy of music therapy on episiotomy wound pain in uncomplicated vaginal deliveries.

Materials and Methods

Subjects

A prospective randomized controlled study was conducted at the Delivery and Postpartum Inpatient Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Srinakharinwirot University, Thailand between March and December 2016. At our institute, all pregnant women were delivered in private room one by one. Uncomplicated singleton vaginal delivery women with the second degree or less episiotomy wound were enrolled into our study. The exclusion criteria were women who received anesthesia more than a local infiltration of xylocaine such as a pudendal nerve block, the presence of birth passage hematoma, cervical tearing requiring surgical suturing, third or fourth degree episiotomy tearing, hearing deficit or impaired balance and allergic to acetaminophen.

Study procedure

The study was approved by the institute ethics committee (SWUEC/E-048/2559) and the Thai Clinical Trials Registry (TCTR 20160325001). During the early active phase of labor, we explained about our study to all singletons which possible to success their deliveries through the vaginal route including how to assess the pain VAS score. Intrapartum management was performed as usual. Immediately after delivery (including placenta), if the physician found a second degree vaginal tear which needed suturing, we asked the patient if she would agree to participant in our study, if she would give her informed consent. Then the participants were randomized into two groups using a computerized block of four. Concealment of allocation was ensured by using serially numbered, sealed opaque envelopes. The envelopes were opened after the informed consent was received by the nurse who prepared the music but was not involved the pain score measurements. The participants' demographic data were collected. Participants were classified into high risk and low risk groups by antenatal history. "High risk" was defined as being complicated with a medical condition such as diabetic

mellitus, hypertension, etc. If none of any complication, we defined as "Low risk". Administration of an analgesic drug during the active 1st stage of labor was recorded. The physician who delivered the baby and sutured the episiotomy wound was blinded to the study. At our hospital, the obstetrician locally injects 1% lidocaine with adrenaline just before performing an episiotomy. Additional injections can be provided during the episiotomy repair at the patient's request because of breakthrough pain. Total lidocaine usage in each participant was recorded. Polyglactin 910 sutures (Vicryl) were used for suturing the episiotomy in all participants. A continuous suturing technique is normally used, although an interrupted suturing technique can be done as indicated for hemostasis. The duration of the episiotomy repair was timed from the first needle puncture until the suture-check rectal examination was finished. The music was introduced as the suturing was finished.

A Yellow Brick Cinema-relaxing piano music with rhythm of 70 beats per minute was used in our study. The music was played through a two-earphone device for the participant in the study groups and the earphones were removed just only for short periods of time (~1 minute) for the participant to complete the VAS evaluations. The music was continued for a full 6 hours postpartum. The compliance of the patient in terms of music listening was monitored by the nurse and number of times the patient discontinued listening more than 30 seconds was recorded. All the participants in both groups received oral acetaminophen 500 milligrams after evaluated pain VAS score at the end of the 2nd hour. If a participant asked for more pain killer than protocol, the episiotomy wound was evaluated and the participant removed from the study.

All participants were asked for a pain VAS assessment at the end of the 2nd and 6th hour after the music started by a nurse who was blinded for the intervention About breast feeding, all pregnant women in our hospital were counseled about breast feeding during the antenatal period, and told that breast feeding should begin as soon as possible following delivery.

During the study, all neonates started breast feeding and room-in with mother after delivery as soon as possible, but following this initial feeding, all participants were asked to delay further breast feeding until after the study ended, 6 hours postpartum. Questions about the level of pain were concentrated on pain at the episiotomy area as much as possible.

Sample size

The study was designed to compare two-independent means formula. From a pilot study, mean ± SD pain VAS were 15.52 ± 16.5 millimeters (mm) and 28.8 ± 21.28 mm in music therapy and control group, respectively. To achieve 80% power, with an alpha equal 0.05, assuming at least 60% retention at the end of the study and a sample ratio between the two groups of 1:1, the sample size required for each group was at least 50 subjects or 100 in total.

Statistical analysis

The statistical analysis was performed with R 2.10.0 software (freeware distributed by the R Development Core Team). The data collected and its distribution was analyzed by Kolmogorov-Smirnov test. Descriptive statistics including number, percentage, median, range, mean, standard deviation (SD) and 95% confidence interval (95% CI) as well as the independent t-test and Mann-Whitney U test were used to detect differences between the VAS scores of the two groups at the end of the 2nd and 6th hours postpartum. A probability value (p value) of < 0.05 was considered significant.

Results

One hundred participants were enrolled in the study, 50 in each group. The participants' baseline characteristics are shown in Table 1. Maternal age, body mass index (BMI), education, parity, gestational age at delivery, degree of episiotomy wound tearing, antenatal risk classification, volume of 1% lidocaine usage, duration of episiotomy wound repairing, history of 1st stage analgesic administration, fetal birth weight and neonatal NICU requirement between the two groups

were not statistically significant. Fortunately, none of our participants needed more pain killer than our protocol or found postpartum hemorrhage or episiotomy wound complication after randomization (Fig. 1).

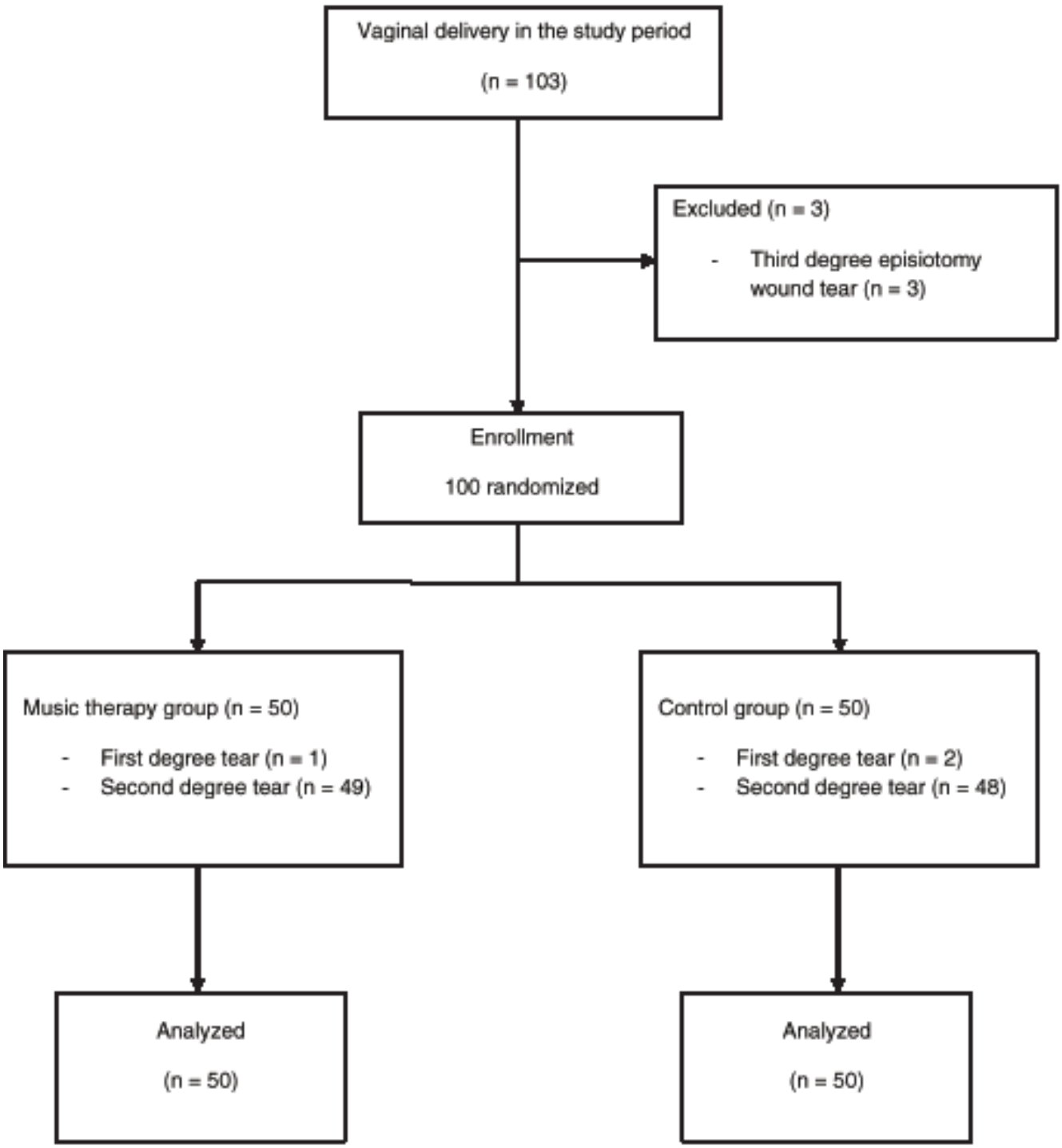

Fig. 1. Randomization.

Table 1. Baseline Characteristics.

Variable	Group	
	Music therapy n = 50	**Control n = 50**
Age (years), mean ± SD	25.9 ± 5.5	25.4 ± 6.2
BMI, kg/m^2, mean ± SD	26.2 ± 4.6	25.9 ± 3.6
Education		
High school and below	36 (72%)	37 (74%)
Bachelor degree and above	14 (28%)	13 (26%)
Parity, n (%)		
Nulliparous	15 (30%)	25 (50%)
Multiparous	35 (70%)	25 (50%)
Gestational age (weeks), mean ± SD	38.8 ± 1.4	30.6 ± 1.5
ANC risk		
Low-risk	36 (72%)	36 (72%)
High-risk	14 (28%)	14 (28%)
1st stage analgesic administration	1 (2%)	2 (4%)
Degree of episiotomy wound tear, n (%)		
First degree	1 (2%)	2 (4%)
Second degree	49 (98%)	48 (96%)
Type of Episiotomy wound		
Median	6 (12%)	5 (10%)
Mediolateral	44 (88%)	45 (90%)
1% lidocaine volume, ml, median (interquartile range)	10 (9-10)	10 (9-10)
Duration of repair episiotomy wound, minutes, median (interquartile range)	30 (20-40)	30 (20-35)
Fetal birth weight, grams, mean ± SD	3009.2 ± 352.8	3033.6 ± 403.9
Neonatal NICU admission, n (%)	5 (10%)	3 (6%)

Table 2. VAS after repair episiotomy.

Pain score	Group		p value
	Music therapy n = 50	**Control n = 50**	
Two-hours after repair episiotomy, (mm), median (interquartile range)	24.0 (8.3-41.5)	36.5 (20.0-53.3)	< 0.001

Table 2 presents the median and interquartile ranges pain VAS scores at the end of the 2nd hour and 6th hour after the repairing process was finished. A median pain VAS scores at the 2nd hour was statistically significantly lower in the music group than in the control group [24.0 mm (8.3-41.5) and 36.5 mm (20.0-53.3), respectively]. A median pain VAS score at the 6th hour was statistically significantly lower in the music group than in the control group [12.0 mm (3.0-21.0) and 22.0 mm (15.0-38.0), respectively].

Discussion

Our study found that the median pain VAS score at the end of 2nd and 6th hour after the repairing process were significant lowered in music therapy using groups. Immediate postpartum pain and discomfort is a quite complex phenomenon. It comprises perineal pain, uterine contraction pain, fatigue and feelings of exhaustion. Perineal pain arises from birth passage trauma and/or following an episiotomy. A higher degree of perineal pain was linked to postpartum dyspareunia and delayed wound healing[10]. Both pharmacologic and non-pharmacological methods have been used for relieving episiotomy pain. Ibuprofen and acetaminophen with codeine can reduce episiotomy wound pain but there were side effects[3]. Cryotherapy using icepacks and epifoam are non-pharmacological methods that have been tried with some success. Icepacks, however, can cause some discomfort because it must directly apply to the perineal area. Music therapy have been found to be an effective alternative treatment for reducing pain in many medical situations such as colonoscopy and burn pain[11, 12]. However, there has been no studied examining the effectiveness of music therapy on reducing postpartum episiotomy wound pain. Thus, our study is the first study conducted with the objective of controlling any factors that might influence the degree of pain following an episiotomy and measuring the pain level by a standard objective method (VAS). The VAS score is an objective tool which is used to measure the degree of pain by asking the participant to indicate a point along a 10 centimeter horizontal line (0 = no pain and 10 = worst possible pain). The VAS has been proven to be an accurate tool for assessing pain in many studies[13]. We found that music therapy was an effective modality for alleviating immediate postpartum episiotomy wound pain at the end of two and six hours post-delivery.

Music can also act as a distraction from pain[11,12]. We believe the main advantage of music therapy over cryotherapy is that there is no need to apply anything directly at the perineum area, which is sensitive from the wound, thus the patient feels more comfortable than with cryotherapy. Unfortunately, a limitation of our study was that we did not assess the patients' satisfaction with the use of music therapy. Moreover, we postulate that both of these mechanisms for reducing pain by music therapy may reduce overall postpartum pain and the discomfort which arises from uterine contractions and anxiety about the new experience in the new mother's life. Also, music has no adverse effects which may accompany pharmacological methods of pain control. Thus, it is a good alternative choice for patients who feel only mild to moderate degrees of pain and want to avoid using pain-relief drugs.

However, our participants were not included severe degree of episiotomy wound. Thus, it limited to confirm about effectiveness. Thus, we plan to evaluate the effectiveness of music therapy on 4th degree episiotomy wounds and also episiotomy wounds with complications such as hematoma or re-suturing. The effectiveness of music therapy in controlling pain longer than 6 hours postpartum should also be investigated, and patients' satisfaction with this form of therapy. Moreover, the method for applying music therapy needs to be investigated, as earphones may be uncomfortable to use and thus lead to lower compliance, and a low level of music in the patient's room may be more suitable for some patients. We also postulate that music may reduce stress and anxiety for other family members, including the newborn him/herself, as a previous study found that music altered the behavior, neural effects, pain response, B-endorphin and cortisol concentrations beginning in the fetal period and carried forward to the newborn period in both term and preterm babies[14-16].

Moreover, we did not confirm the baseline VAS scores before the intervention because we believed that it should be approximately equal by randomization. Thus, it may be a weakness of our study. Compare to previous study which evaluate the pain VAS score after using music for reducing pain in the management of chronic pelvic pain. It found that music could be a more significant reduction in VAS pain between study and control group (3 ± 1.7 VS 4.6 ± 1.7, respectively) and reducing both anxiety/depression[17]. Even the level of pain VAS score before and after using the intervention are not very different but the pain is a complex feeling. Thus the authors believe that decreasing of pain at any level make the patients feel better.

Conclusion

In conclusion, music therapy is an effective alternative modality for alleviating during the first 6 hours postpartum episiotomy pain without side effects.

Acknowledgments

The authors would like to thank the Office of International Affairs of the Faculty of Medicine, Prince of Songkla University, for editorial assistance

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Carroli G, Mignini L. Episiotomy for vaginal birth. Cochrane Database Syst Rev 2009,1:CD000081.
2. Chayachinda C, Titapant V, Ungkanungdecha A. Dyspareunia and sexual dysfunction after vaginal delivery in Thai primiparous women with episiotomy. J Sex Med 2015;12:1275-82.
3. Peter EA, Janssen PA, Grange CS, Douglas MJ. Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. CMAJ 2001;165:1203-9.
4. Kargar R, Aghazageh-Nainie A, Khoddami-Vishteh HR. Comparison of the effects of lidocaine prilocaine cream (EMLA) and lidocaine injection on reduction of perineal pain during perineum repair in normal delivery. Family Reprod Health 2016;10:21-6.
5. Graversen M, Sommer T. Perioperative music may reduce pain and fatique in patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2013;57:1010-6.
6. Ozer N, Karaman Ozlu Z, Arslan S, Gunes N. Effect of music on postoperative pain and physiologic parameters of patients after open heart surgery. Pain Mang Nurs 2013;14:20-8.
7. Good M, Anderson GC, Stanton-Hicks M. Relaxation and music therapy reduce pain after gynecologic surgery. Pain Manag Nurs 2002;3:61-70.
8. Phumdoung S, Good M. Music reduces sensation and distress of labor pain. Pain Manag Nurs 2003;4:54-61.
9. Allred KF, Byers JF, Sole ML. The effect of music on postoperative pain and anxiety. Pain Manag Nurs 2010;11:15-25.
10. Steen M, Cooper K, Marchant P, Griffiths-Jones M, Walker J. A randomized controlled trial to compare the effectiveness of icepacks and epifoam with cooling maternity gel pads at alleviating postnatal perineal trauma. Midwifery 2000;16:48-55.
11. De Silva AP, Niriella MA, Nandamuni Y, Nanayakkara SD, Perera KR, Kodisinghe SK, et al. Effect of audio and visual distraction on patients undergoing colonoscopy: a randomized controlled study. Endosc Int Open 2016;4:1211-4.
12. Najafi Ghezeljeh T, Mohades Ardebili F, Rafii F. The effects of massage and music on pain, anxiety and relaxation in burn patients: randomized controlled trial. Burns 2017;43:1034-43
13. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: visual analog scale for pain (VAS pain), numeric rating scale for pain (NRS pain), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63:240-52.
14. James DK, Spancer CJ, Stepsis BW. Fetal learning: a prospective randomized controlled study. Ultrasound Obstet Gynecol 2002;20:431-8.
15. Partanen E, Kujala T, Tervaniemi M, Huotilainen M. Prenatal music exposure induces long-term neural effects. PLoS One 2013;30:e78946.
16. Qiu J, Jiang YF, Li F, Tong QH, Rong H, Cheng R. Effect of combined music and touch intervention on pain response and β-endorphin and cortisol concentrations in late preterm infants. BMC Pediatr 2017;17:38.
17. Guetin S, Ginies P, Siou DK, Picot MC, Pommie C, Guldner E, et al, The effects of music intervention in the management of chronic pain: a single-blind, randomized, controlled trial. Clin J Pain 2012;28:329-37.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No.3, pp. 166-174

OBSTETRICS

Estimating the Date of Confinement: A 3-year Retrospective Study in Ramathibodi Hospital

Nattaporn Poopaibool, M.D.*,
Sommart Bumrungphuet, M.D.*,
Nathpong Israngura Na Ayudhya, MD., MSc (Clin Epi)*.

** Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, 10400, Thailand*

ABSTRACT

Objectives: To estimate limits of agreement (LOA) between the actual date of delivery (ADD) and four different methods for estimated date of confinement (EDC) based on last menstrual period (LMP).

Materials and Methods: This retrospective cross-sectional study was conducted in the pregnant women who delivered at Ramathibodi Hospital, Bangkok, Thailand during 2013-2015. The inclusion criteria were term pregnancy, singleton, spontaneous onset of labor, certain date and duration of LMP, regular menstrual cycles, no recent use of hormonal contraceptives in past 3 months, ultrasound scan in mid-trimester was performed and all newborns were evaluated full-term by pediatricians. Exclusion criteria was wrong date recalled after redating with ultrasound scan in mid-trimester. Four methods for EDC: Naegele's rule using the 1st day of LMP, Naegele's rule using last day of LMP, pregnancy wheel, and pregnancy calculator application were compared with ADD. The discrepancies between EDC and ADD were defined as the LOA and its 95% confidence interval (95%CI). Statistical comparison was performed by using Bland and Altman's method.

Results: There were 1,883 pregnant women who met the criteria. LOA of ADD was 5.2 days before predicted EDC by pregnancy calculator application. Predicted EDC using last day of LMP by Naegele's rule was differ from LOA of ADD more than other methods (-8.8 days). Different days in each month affect predicted EDC except by application method.

Conclusion: Pregnancy calculator application based on LMP is the preferred method for predicting EDC when compared with Naegele's rule and pregnancy wheel in women who can certainly remember her LMP.

Keywords: EDC, Estimated date of delivery, Naegele's rule, pregnancy wheel, pregnancy calculator application

Correspondence to: *Nattaporn Poopaibool, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, 270 Rama 6 Rd., Ratchathewi, Bangkok, 10400 Thailand.*
Tel: 66-8-1-9286987, Email address: npsound20@gmail.com

การคาดคะเนกำหนดคลอด การศึกษาย้อนหลัง 3 ปีในโรงพยาบาลรามาธิบดี

ณัฐพร ภู่ไพบูลย์, สมมาตร บำรุงพืช, ณัฐพงศ์ อิศรางกูร ณ อยุธยา

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษา limits of agreement ระหว่างวันคลอดจริงกับกำหนดคลอดจากการคำนวณที่แตกต่างกัน 4 วิธี โดยนับจากประจำเดือนครั้งสุดท้าย

วัสดุและวิธีการ: การศึกษาย้อนหลังในหญิงตั้งครรภ์ที่คลอดในโรงพยาบาลรามาธิบดี ช่วงระหว่างมกราคม พ.ศ.2556 ถึง ธันวาคม พ.ศ.2558 โดยมีเกณฑ์การคัดเข้าคือ หญิงตั้งครรภ์เดี่ยว ครบกำหนด เจ็บครรภ์คลอดเองตามธรรมชาติ จำวันและระยะเวลาของประจำเดือนครั้งสุดท้ายได้แม่นยำ ประจำเดือนมาสม่ำเสมอ ไม่มีประวัติใช้ฮอร์โมนคุมกำเนิดในช่วงสามเดือนก่อนการตั้งครรภ์ ได้รับการอัลตราซาวน์ในช่วงไตรมาสที่สองของการตั้งครรภ์ และทารกอายุครบกำหนดคลอดจากบันทึกของกุมารแพทย์ เกณฑ์การคัดออกคือ กำหนดคลอดที่เปลี่ยนโดยอัลตราซาวน์ในช่วงไตรมาสที่สองเนื่องจากจำประจำเดือนครั้งสุดท้ายผิด จากนั้นคำนวณวันคลอดโดยสี่วิธี คือ 1. กฎของ Naegele โดยใช้วันแรกของประจำเดือนครั้งสุดท้าย 2. กฎของ Naegele โดยใช้วันสุดท้ายของประจำเดือนครั้งสุดท้าย 3. วงล้อหมุน 4. แอปพลิเคชั่น นำมาเปรียบเทียบกับวันคลอดจริง ความแตกต่างระหว่างกำหนดคลอดที่คำนวณได้กับวันคลอดจริงกำหนดให้เป็นระดับข้อตกลง และความเชื่อมั่น 95 เปอร์เซ็นต์ เปรียบเทียบค่าทางสถิติโดยใช้วิธีของ Bland และ Altman

ผลการวิจัย: จากหญิงตั้งครรภ์ที่คลอดทั้งหมด 1,883 รายที่เข้าเกณฑ์ วิธีคำนวณกำหนดคลอดโดยใช้แอปพลิเคชั่นใกล้เคียงวันคลอดจริงมากที่สุด คือ หลังวันคลอดจริง 5.2 วัน ในขณะที่วิธีคำนวณโดยกฎของ Naegele จากวันสุดท้ายของประจำเดือนครั้งสุดท้ายห่างจากวันคลอดจริงมากที่สุด คือ หลังวันคลอดจริง 8.8 วัน จำนวนวันที่ต่างกันในแต่ละเดือนมีผลต่อการคำนวณกำหนดคลอด แต่จะไม่มีผลกระทบต่อวิธีคำนวณโดยใช้แอปพลิเคชั่น

สรุป: แอปพลิเคชั่นคำนวณกำหนดคลอดจากประจำเดือนครั้งสุดท้ายเป็นวิธีที่ดีกว่าเมื่อเทียบกับการใช้กฎของ Naegele และวงล้อหมุนในหญิงตั้งครรภ์ที่จำประจำเดือนครั้งสุดท้ายได้แม่นยำ

คำสำคัญ: กำหนดคลอด, กฎของ Naegele, วงล้อคำนวณวันคลอด, แอปพลิเคชั่นคำนวณวันคลอด

Introduction

The accurate determination of gestational age is very important in prenatal care and the time of delivery management. These include screening for fetal aneuploidy, intervention at the limit of fetal viability, the administration of corticosteroids for fetal lung maturation, and the elective induction of labor in some indicated conditions in order to decrease both mother and fetal morbidity and mortality e.g. hypertension, diabetes, and postterm pregnancy. Nowadays, the ultrasound measurement of embryo or fetus in the 1st trimester is the most accurate method to establish or confirm gestational age[1]. However, last menstrual period (LMP) is still important in clinical practice, physicians use various methods to calculate estimated date of confinement (EDC) from LMP depending on their preferred methods, such as Naegele's rule, pregnancy wheel or pregnancy calculator application. The discrepancies of EDC between each method can affect the management and the outcome of pregnancy.

In general, gestational age will be corrected by ultrasound if EDC discrepancies are more than determined days[2], the reliability of ultrasound will be decreased depending on the time of first ultrasound performed. At Ramathibodi hospital, if the height of fundus from physical examination correlates with gestational age by certain LMP, obstetricians usually wait until mid-trimester to perform ultrasound screening for fetal anomaly and correcting the gestational age. However, in some parts of Thailand, especially in the setting of community hospitals, insufficient resources and healthcare providers are the major problems and ultrasound may be performed later than usual in some women. This results in the discrepancies between EDC by LMP and ultrasound which can be extended to more than 14 days, especially in the case of suboptimally dated pregnancies[3].

The duration of pregnancy is 280 days from the onset of LMP or 266 days from the date of conception. Naegale's rule assumes a 28-day-cycle with ovulation on day fourteen. By adding 7 days to the first day of the last menstrual period and counting back 3 months the expected date of confinement can be obtained. But the duration of pregnancy by Naegale's rule is not always exactly 280 days, due to the number of days in each month[4]. The largest published cohort study of 427,582 singleton pregnancies in Sweden showed that the average duration from LMP to vaginal birth was 281 days (mean), 282 days (median), and 283 days (mode)[5].

As Baskett et al. stated, Naegale did not the first person who invented the rule[6,7]. It may have been the famous Hermann Boerhaave (1668-1738), Professor of Botany and Medicine at Leyden University, who first set down this calculation. Franz Carl Naegele (1778-1851), Professor of Obstetrics at the University of Heidelberg, also quoted Boerhaave's section in his 1812 textbook. Baskett et al., commented that their wording "counting from the last menstrual period" lacked of precision, so that one could interpret conception as the occurrence either seven days after the start or after the end of the last period. Bedford, the Professor of Obstetrics and Diseases of Women and Children in the University of New York, did so in his 1872 text, he had taken the date to which the seven days should be added as the end of the period[8]. The calculation "from the last menstrual period" remained unclear until the late 19th and early in the 20th century, the standard American texts advocated Naegele's rule which were interpreted as adding seven days to the start of the last menstrual period[9].

In common obstetric practice, a pregnancy wheel is usually used for calculating the gestational age based on the normal duration of pregnancy of 280 days. In addition, pregnancy calculator application becomes more widespread along with the introduction of smartphones and tablets. The convenience and functionality of these devices offer their popularity among users.

Despite the accuracy of pregnancy dating by ultrasound, physicians commonly use alternative methods for assessing gestational age at each antenatal care visit. But there remains doubtful which methods would be the best among these methods for the estimated delivery date calculation based on LMP.

This study aimed to determine the precision of four methods: by Naegele's rule using the 1st day of LMP, by Naegele's rule using last day of LMP, using pregnancy wheel, and using pregnancy calculator application, in predicting term gestation when compared with the actual date of delivery.

Materials and Methods

From January 2013 to December 2015, data from total 7,514 unselected deliveries in Ramathibodi Hospital were retrospectively collected. The inclusion criteria were term pregnancy (gestational age 370/7-416/7 weeks), singleton, spontaneous onset of labor, certain date and duration of LMP, regular menstrual cycle with interval 21-35 days (LMP, previous menstrual period and duration of period were recorded), no recent use of hormonal contraceptives in past 3 months, ultrasound measure for gestational age in mid-trimester was performed and all newborns were evaluated full-term by pediatricians. From the remaining 2,767 women, 884 women were excluded due to wrong date recalled after redating with ultrasound scan in mid-trimester. The final study population thus comprised of 1,883 women, as shown in Fig. 1. No pregnancy from assisted reproductive technology was included in this study.

EDC were calculated by 4 methods for each woman: (1) Naegele's rule by the 1st day of LMP (2) Naegele's rule by the last day of LMP (3) pregnancy wheel and (4) pregnancy calculator application.

The duration of normal pregnancy was defined as 280 days. The accuracy in predicting the EDC was calculated for term deliveries only because preterm delivery was a unique condition that caused by various pathologic processes which may affect to the results. For this reason, this group was not included in the study.

Naegele's rule was used to calculate EDC by adding 7 days and counting back 3 months from the 1st day of LMP (EDC1) and calculated from the last day of LMP (EDC2). EDC Wheel was calculated by using pregnancy wheel based on the normal duration of pregnancy of 280 days. We use only one wheel by one observer to reduce inter-observer variability. There were 365 tick marks in the wheel and numbers of tick marks were corresponded with the month. If a wheel EDC was midway between two dates, the later date was used. However, there was no scoring system for pregnancy wheel. Finally, the manual pregnancy wheel that was commonly used in antenatal clinic manufactured by Obimin AZ® was chosen for this study. The pregnancy calculator application was used to calculate EDC App by using the 280 day rule from 1st day of LMP. According to APPLICATIONS Scoring System[10], ACOG EDD calculator was selected for this study because of the highest score among all of the other pregnancy calculator apps (score 13 out of 16)[11].

Sample size was calculated using data from pilot study of 40 women to estimate limits of agreement (LOA) between predicted EDC and actual date of delivery (ADD). The sample size can be estimated based on the equation for estimation of lower limit (LL) and upper limit (UL) of 95% confidence interval (95%CI) of LOA, with varying delta (confidence interval width). The estimated SD of delta (ADD-EDC2) is 9.38. Delta equaled 2 was chosen and sample size of 760 women were calculated.

Describe data by means or median where appropriate for continuous data and frequency for categorical data. Estimated limits of agreement and its 95% CI were calculated by Bland and Altman's method[12,13]. Duration of pregnancy was defined as duration between LMP and predicted EDC. All analyses were performed by STATA 14.2.

The study was approved by the Center of Ethical Reinforcement for Human Research, Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID 05-59-25).

Results

Demographic characteristics are shown in Table 1. Mean age was 29.1 years (SD 5.8 years) and mean pre-pregnant BMI was 21.3 kg/m^2 (SD 3.6 kg/m^2). Most women were primigravida (61.7%). Mean birthweight of newborn were 3,137.9 g (SD 372.8 g) and percentage of newborn's sex was comparable (49.8% vs 50.2%).

Table 1. Demographic characteristics.

Characteristics	No.	Percent
Age (years), mean ± SD	29.1 ± 5.8	
Prepregnant BMI (kg/m^2), mean ± SD	21.3 ± 3.6	
Parity:		
0	1,162	61.7
1	542	28.8
≥ 2	179	9.5
Route of delivery:		
Normal labor	1,233	65.5
Cesarean section	572	30.4
Vacuum extraction	53	2.8
Forceps extraction	25	1.3
Newborn:		
Birth weight (grams), mean ± SD	3,137.9 ± 372.8	
Sex		
Male	938	49.8
Female	945	50.2

Fig. 2. shows difference in days between predicted EDC1 and average ADD presented as LOA and 95%CI in Bland-Altman's plot. The mean difference was -6.0 days (average ADD occurred before predicted EDC1 for 6 days) with 95%CI -20.1 to 8.1 days. Fig. 3. presents LOA and 95%CI of all 4 methods. Average ADD usually occurred before predicted EDCs. LOA was about 5 days before predicted EDC by pregnancy calculator application with a range of -19.3 to 8.8 days which was closer to LOA of ADD than other methods. LOA by pregnancy wheel and Naegele's rule using the 1st day of LMP were relatively equal 6 days before predicted EDC (-5.9 and -6.0 days, respectively). The use of the last day of LMP by Naegele's rule was differed from LOA of ADD more than other methods (-8.8 days).

Seasonal variability in mean duration of pregnancy by each method was observed but this was found to be consistent with EDC by pregnancy calculator application (Fig. 4).

Discussion

Accurate determination of gestational age is very important in prenatal care. There were many methods used in predicting EDC based on LMP. The discrepancy of EDC between each method may confound the physicians and lead to inaccurate gestational age determination. The results in this study suggested that EDC by using pregnancy calculator application was the most accurate whereas EDC by using the last day of LMP was the least accurate among 4 methods when compared with ADD.

In population of women whose the LMP were known, EDC based on LMP were 3.3 days earlier[14]. Oslen et al claimed that if 283 days were added to the LMP would render the EDC based on LMP estimates more accurate[15]. Similarly, the mode (283 days) estimated in duration of pregnancy from the Swedish birth registry was felt to be more accurate than the mean value (280 days) as it reduced the influence of pathological pregnancies at the extreme of prematurity[5]. Baskett et al .,concluded that original Naegale's rule may have to add seven days to the end instead of the beginning of the LMP[6].

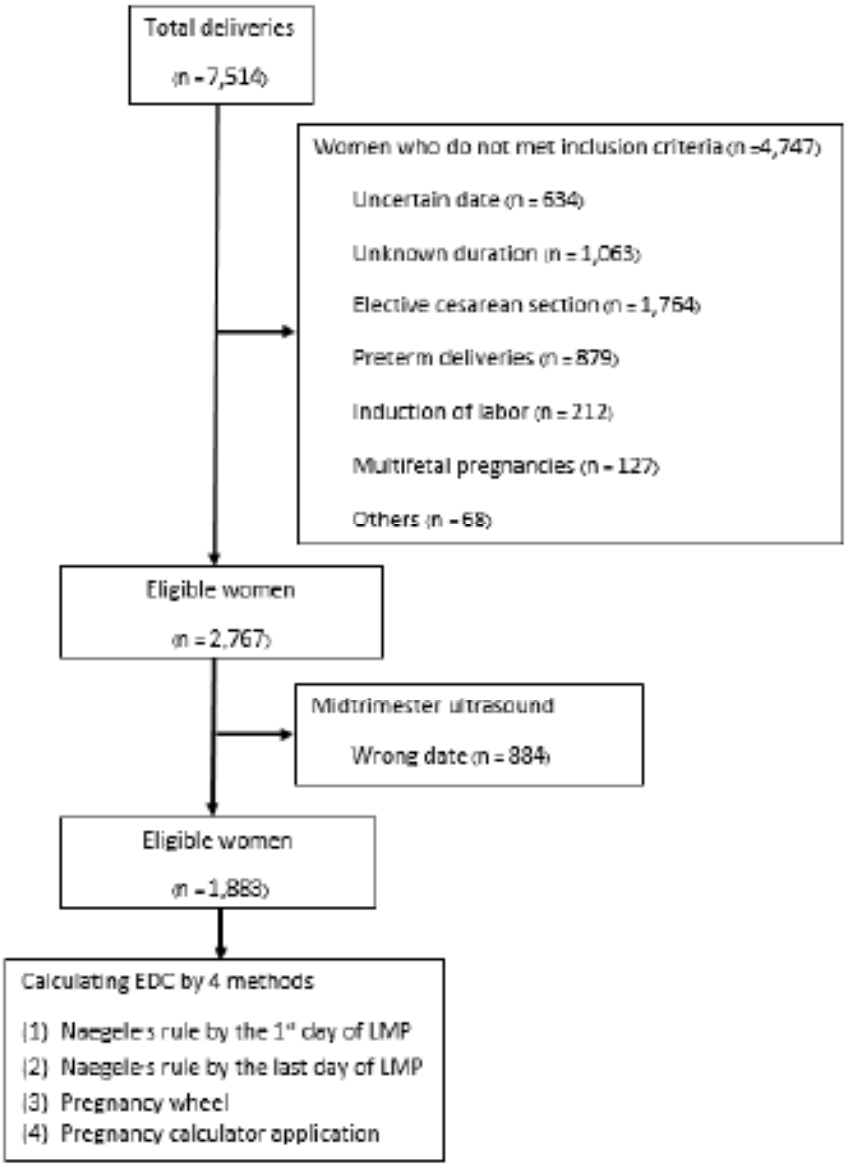

Fig. 1. Flow chart of analytic sample selection.

The results of this study did not support Baskett et al.'s conclusion. EDC by Naegele's rule calculated from last day of LMP was different from ADD when compared with EDC calculated from 1st day of LMP (8.8 vs 6.0 days). This may result from last day of LMP were varied in individuals, uncertain duration of menstrual cycle and amount of menstruation which effected in marked variations in range of EDC.

Ross found discordance between the EDC determined by wheels and the computerized program up to five days[16], whereas McParland et al quote the inter-wheel variation was up to seven days between different manufacturers[17]. Hutchon et al compared an obstetrical wheel and ultrasound dating among seventeen obstetricians and concluded that concordance and accuracy would be improved with a computer-based system[18]. Linda et al., evaluated electronic applications and paper pregnancy wheels

and found that the largest discrepancy was four days short of 280 days in the later group[19].

This study results showed that predicted EDC by pregnancy calculator application was close to ADD more than other methods, similar to previous studies. Seasonal variability was clearly seen from Naegele's rule calculation which was similar to pregnancy wheel. Because of calculation by adding and subtracting method was imprecise by different number of days in a month while the length of pregnancy always consistent with 280 days in pregnancy calculator application. Moreover, applications have no limitation like pregnancy wheel. As noted by McParland and Johnson[17], the alignment of wheels may not be concentric, and central mounting may be loosen, even though this was not detected by inspection. Physicians should be aware of the potential error of both Naegale's rule and pregnancy wheels.

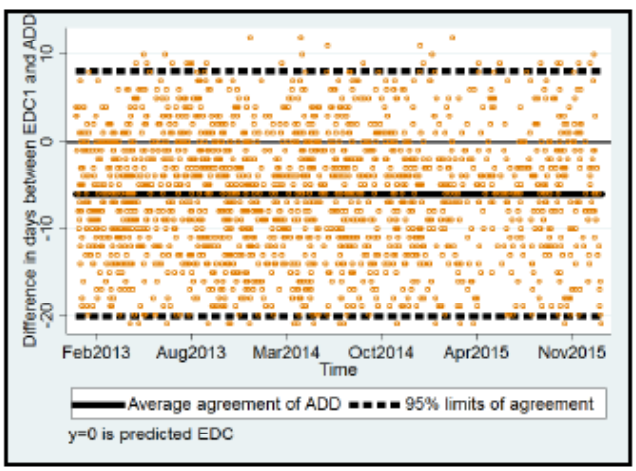

Fig. 2. Difference in days between predicted EDC1 and average ADD.

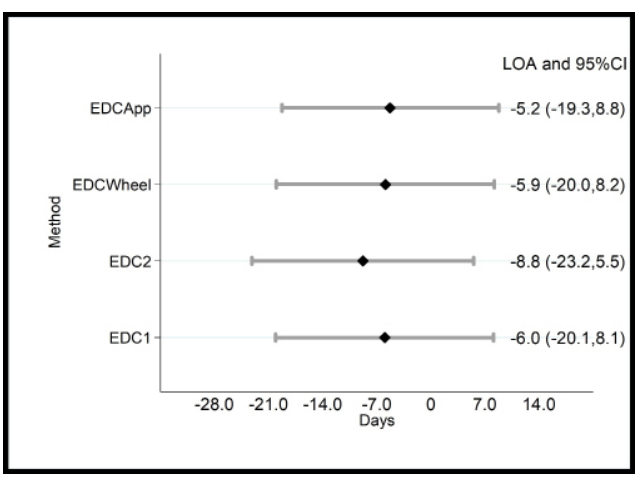

Fig. 3. Limits of agreement between actual date of delivery and predicted EDCs. EDC1; Naegele's rule by the 1st day of LMP. EDC2; Naegele's rule by the last day of LMP, EDC Wheel; pregnancy wheel, EDC App; pregnancy calculator application, Day 0 = predicted EDC.

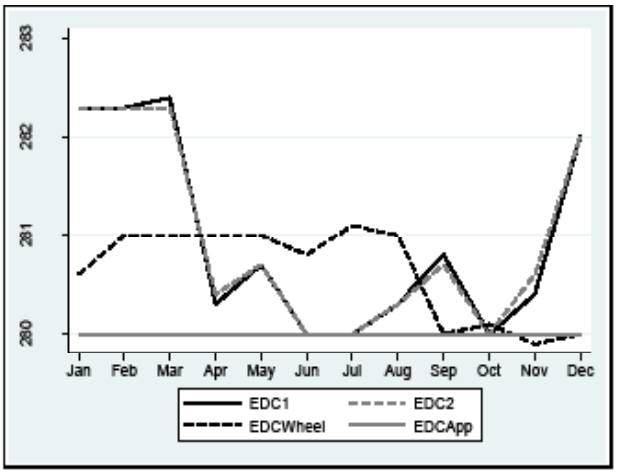

Fig. 4. Seasonal variability in mean duration of pregnancy by each method. EDC1; Naegele's rule by the 1st day of LMP. EDC2; Naegele's rule by the last day of LMP, EDC Wheel; pregnancy wheel, EDC App; pregnancy calculator application.

However, several factors may limit the accuracy of EDC base on LMP, such as women who do not have regular 28-day cycle due to variability in the length of the follicular phase, the fertile window which may not day 14, variations of the duration between fertilization and implantation, and uncertain date of their last period[20]. Therefore, physicians should be aware of predicting EDC based on LMP alone and ultrasound redating is necessary for EDC confirmation. Nevertheless, limitation of healthcare resource in Thailand, especially in countryside, only few women had ultrasound scan in the first trimester for indicated obstetric conditions such as first trimester bleeding, uncertain menstrual date, etc. This suggests that LMP is still important in predicting EDC in common clinical practice in Thailand.

The strength of this study were enrollment only women who can certainly remember her LMP and previous menstrual period which can identify regularity of menstrual cycle and duration of period, and all of them were performed ultrasound screening in the mid-trimester to confirm EDC. But there were some limitations included retrospective study, exclusion of more than 70% of women because of uncertain date and intervention for delivery and did not include a leap year in this study.

Conclusion

Pregnancy calculator application was preferred for predicting EDC based on LMP when compared with Naegele's rule and pregnancy wheel in women who could certainly remember her LMP.

Acknowledgements

We are grateful to Assoc. Prof. Dr. Ammarin Thakkinstian and Sukanya Siriyotha, Clinical Epidemiology and Biostatistics Section, Faculty of Medicine Ramathibodi Hospital, Mahidol University for their contribution in the statistical analysis. We would like to thank all the staff of the Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University for their support in this study.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Caughey AB, Nicholson JM, and Washington AE. First-

vs second-trimester ultrasound: the effect on pregnancy dating and perinatal outcomes. Am J Obstet Gynecol 2008;198:703. e1-703.e6.
2. American College of Obstetricians and Gynecologists. Method for estimating due date. Committee Opinion No. 611. Obstet Gynecol 2014;124:863-6.
3. American College of Obstetricians and Gynecologists. Management of suboptimally dated pregnancies. Committee Opinion No. 688. Obstet Gynecol 2017;129: 591-2.
4. Nguyen TH, Larsen T, Engholm G, MØller H. Evaluation of ultrasound-estimated date of delivery in 17,450 spontaneous singleton births: do we need to modify Naegele's rule?. Ultrasound Obstet Gynecol 1999;14: 23-8.
5. BergsjØ P, Denman DW, Hoffman HJ, Meirik O. Duration of human singleton pregnancy – a population-based study. Acta Obstet Gynaecol Scand 1990; 69: 197-207.
6. Baskett TF, Nagele F. Naegele's rule: a reappraisal. Br J Obstet Gynaecol 2000;107:1433-5.
7. Loytved CAL, Fleming V. Naegele's rule revisited. Sex Reprod Healthc 2016;8:100-1.
8. Bedford GS. The Principles and Practice of Obstetrics. 5th Edition. New York: William Wood and Co, 1872: 306.
9. Williams JW. Obstetrics. New York: D. Appleton & Co, 1903:171-4.
10. Chyjek K, Farag S, Chen KT. Rating pregnancy wheel applications using the APPLICATIONS Scoring System. Obstet Gynecol 2015;125:1478-83.
11. ACOG reinvents the pregnancy wheel. American College of Obstetricians and Gynecologists [Internet]. 2016 [cited 2016 Jan 22] Available from: https://m.acog.org/About-ACOG/News-Room/News-Releases /2016/ACOG-Reinvents-the-Pregnancy-Wheel?IsMobileSet=true
12. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1:307-10.
13. Bland JM, Altman DG. Applying the right statistics: analyses of measurement studies. Ultrasound Obstet Gynecol 2003;22:85-93.
14. Backe B, Nakling J. Term prediction in routine ultrasound practice. Acta Obstet Gynaecol Scand 1994; 73:113-8.
15. Olsen O, Aaroe Clausen J. Routine ultrasound dating has not been shown to be more accurate than the calendar method. Br J Obstet Gynaecol 1997;107: 1221-2.
16. Ross MG. Circle of time: errors in the use of the pregnancy wheel. J Matern Fetal Neonatal Med 2003; 14:370-2.
17. McParland P, Johnson H. Time to reinvent the wheel. Br J Obstet Gynaecol 1993;100:1061-2.
18. Hutchon DJ, Kearney C. Clinical interpretation of ultrasound biometry for dating and for assessment of fetal growth using a wheel and chart: is it sufficiently accurate? Ultrasound Obstet Gynecol 1999; 13: 103-6.
19. Chambliss LR, Clark SL. Paper gestational age wheels are generally inaccurate. Am J Obstet Gynecol 2014; 210:145. e1-4.
20. Mackenzie AP, Stephenson CD, Funai EF. Prenatal assessment of gestational age and estimated date of delivery. Uptodate [Internet]. 2016 [cited 2016 Apr 8] Available from: http://www.uptodate.com/contents/prenatal-assessment-of-gestational-age-and-estimated-date-of-delivery.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 175-181

OBSTETRICS

Risk Factors for the Occurrence of Scalp Hematoma in Term Neonates in King Chulalongkorn Memorial Hospital

Chaiyawut Paiboonborirak, M.D.*,
Anongnart Sirisabya, M.D.**,
Yada Kunpalin, M.D.*,
Surasith Chaithongwongwatthana, M.D., M.Sc.*.

** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.*
*** Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.*

ABSTRACT

Objectives: To determine the incidence and associated factors of neonatal scalp hematoma.

Materials and Methods: This prospective case-control study included all term singleton live newborns that delivered in King Chulalongkorn Memorial Hospital during July 2016 to October 2016. All neonates were prospectively evaluated and divided into two groups: cases with scalp hematoma and controls. Diagnoses of neonatal scalp hematoma either cephalhematoma or subgaleal hemorrhage were confirmed by the experienced neonatologist. Medical records of these neonates and their mothers were reviewed to collect demographic data and information regarding their processes of labor and delivery. Logistic regression analysis was used to identify the risk factors associated with presence of neonatal scalp hematoma.

Results: A total of 938 term neonates were included in this study. The incidence of neonatal scalp hematoma was 3.19% (30/938). Operative obstetrics (vacuum and forceps extraction) were found to have the highest rate (15.38%) of scalp hematoma when compare with other routes of delivery. Factors associated with neonatal scalp hematoma were primiparity (adjusted OR 4.86, 95% CI 1.61-14.58) and prolonged second stage of labor (adjusted OR 4.31, 95% CI 1.08-17.25). When analysis was done in only vaginally delivered neonates, the significant factors were primiparity (adjusted OR 3.84, 95% CI 1.26-11.71) and artificial rupture of membranes (adjusted OR 2.93, 95% CI 1.24-6.97).

Conclusion: Neonatal scalp hematoma was common. Primiparous women significantly increased risk of neonatal scalp hematoma regardless of route of delivery.

Keywords: birth injury, cephalhematoma, subgaleal hemorrhage, term neonate

Correspondence to: *Surasith Chaithongwongwatthana, M.D., M.Sc., Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Tel: 66-2-2564000, Fax: 66-2-2524963, Email address: iamsurasith@gmail.com*

ปัจจัยเสี่ยงที่สัมพันธ์กับการเกิดก้อนเลือดออกในชั้นหนังศีรษะของทารกแรกเกิดคลอดครบกำหนดในโรงพยาบาลจุฬาลงกรณ์

ชัยวุฒ ไพบูลย์บริรักษ์, อนงค์นาถ ศิริทรัพย์, ญดา คุนผลิน, สุรสิทธิ์ ชัยทองวงศ์วัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์และปัจจัยที่สัมพันธ์กับการเกิดภาวะก้อนเลือดออกในชั้นหนังศีรษะของทารกที่คลอดครบกำหนด*

ระเบียบงานวิจัย: *การศึกษานี้เป็นการศึกษาไปข้างหน้าแบบมีกลุ่มควบคุม ที่รวบรวมทารกคลอดครบกำหนดทุกรายที่เกิดในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่เดือนกรกฎาคม พ.ศ.2559 ถึงเดือนตุลาคม พ.ศ.2559 ทารกที่คลอดครบกำหนดทุกรายจะถูกแบ่งออกเป็น 2 กลุ่ม ได้แก่ กลุ่มที่มีภาวะก้อนเลือดออกในชั้นหนังศีรษะ และอีกกลุ่มคือกลุ่มควบคุม โดยทารกที่มีภาวะก้อนเลือดออกในชั้นหนังศีรษะไม่ว่าจะเป็นภาวะ Cephalhematoma หรือ Subgaleal hemorrhage ได้รับการยืนยันการวินิจฉัยจากแพทย์ผู้เชี่ยวชาญด้านทารกปริกำเนิด มีการเก็บรวมรวมข้อมูลจากเวชระเบียนในส่วนของประวัติการตั้งครรภ์ และรายละเอียดของการคลอดบุตร ใช้การวิเคราะห์ Logistic regression เพื่อหาปัจจัยที่มีผลต่อการเกิดภาวะก้อนเลือดออกในชั้นหนังศีรษะของทารกแรกเกิด*

ผลการศึกษา: *จากทารกคลอดครบกำหนดทั้งหมด 938 ราย พบว่า อุบัติการณ์การเกิดก้อนเลือดออกในชั้นหนังศีรษะเท่ากับร้อยละ 3.19 (30/938) เมื่อเปรียบเทียบกับการคลอดวิธีอื่น พบว่าการใช้สูติศาสตร์หัตถการ (vacuum and forceps extraction) มีอุบัติการณ์การเกิดก้อนเลือดออกในชั้นหนังศีรษะสูงสุด คือ ร้อยละ 15.38 โดยปัจจัยที่สัมพันธ์กับการเกิดก้อนเลือดออกในชั้นหนังศีรษะในการศึกษานี้ ได้แก่ การคลอดบุตรครั้งแรก (adjusted OR 4.86, 95% CI 1.61-14.58) และภาวะการคลอดระยะที่สองนานกว่าปกติ (adjusted OR 4.31, 95% CI 1.08-17.25). เมื่อวิเคราะห์ข้อมูลในกลุ่มที่คลอดทางช่องคลอดเท่านั้น พบว่า การคลอดบุตรครั้งแรก และการเจาะถุงน้ำคร่ำ สัมพันธ์กับการเกิดภาวะก้อนเลือดออกในชั้นหนังศีรษะอย่างมีนัยสำคัญทางสถิติ (adjusted OR 3.84, 95% CI 1.26-11.71 และ 2.93, 95% CI 1.24-6.97 ตามลำดับ)*

สรุป: *ภาวะเลือดออกใต้ชั้นหนังศีรษะเป็นภาวะที่พบได้บ่อย โดยการคลอดบุตรครั้งแรก เพิ่มความเสี่ยงในการเกิดภาวะก้อนเลือดออกในชั้นหนังศีรษะโดยไม่ว่าจะเป็นการคลอดโดยช่องทางใดก็ตาม*

คำสำคัญ: *การบาดเจ็บจากการคลอดบุตร, ภาวะก้อนเลือดในชั้นใต้เยื่อหุ้มกะโหลกศีรษะ, ภาวะก้อนเลือดระหว่างพังผืดของกะโหลกกับเยื่อหุ้มกะโหลกศีรษะ, ทารกแรกเกิดคลอดครบกำหนด*

Introduction

Neonatal birth injury is defined as the structural or functional damage of the neonate's body due to traumatic events during labor and delivery[1]. It does not only cause infant morbidities, but may also lead to various consequences such as prolonged hospital stay, increased cost of treatment, parental emotional effects, child disability, and perinatal death. The incidence of neonatal birth injury has decreased over time with advancement of obstetric care; however, it has still been estimated to appear in 2-7% of all deliveries[2]. The most frequently diagnosed birth injury was injuries to the scalp and causing neonatal scalp hematoma[2,3].

Neonatal scalp hematoma or extracranial hematoma is the blood collection outside the calvarium and categorized as cephalhematoma or subgaleal hemorrhage. Cephalhematoma is a subperiosteal collection of blood between the dense fibrous periosteal tissue covering the skull and the skull[1,4]. It is usually benign condition which resolves spontaneously without any treatment[5]. Differently, subgaleal hemorrhage is bleeding between the galea aponeurotica and periosteum of skull[1,4]; 25-33% of cases may be severe and life-threatening[6].

Most of the previous studies regarding neonatal birth injury reviewed the databases or medical records for diagnosing the injuries[2,3,7] that may lead to underestimate or overestimate the number of neonates complicated with scalp hematoma. This study was conducted to determine the incidence and associated risk factors of scalp hematoma in term neonates with prospective and validated evaluation of all recruited infants.

Materials and Methods

The study was approved by ethic committee of The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, in compliance with the International guidelines for human research protection as Declaration of Helsinki, The Belmont Repost, The Council for International Organizations of Medical Sciences (CIOMS) Guideline and International Conference on Harmonization in Good Clinical Practice (ICH-GCP). This prospective case-control study included term (≥ 37 weeks of gestation) singleton live-born neonates that delivered in King Chulalongkorn Memorial Hospital between July and October 2016. Newborns who either non-vertex delivered, had major anomalies, bleeding disorders, or born before arrival were excluded. All recruited neonates were examined by neonatologists and divided into two groups either case with scalp hematoma or control. Because the hematoma could develop a few days after birth, the neonates were reexamined before they were discharged from the hospital. Cases with scalp hematoma were evaluated and confirmed by experienced neonatologist.

Scalp hematoma in this study was diagnosed clinically and categorized as a cephalhematoma or subgaleal hemorrhage. Cephalhematoma was diagnosed when presence of a firm tense mass with a palpable rim that localized over one area of the skull and not across the suture[8]. Subgaleal hemorrhage was diagnosed when presence of a fluctuating mass that straddles cranial sutures or fontanelles[8]. Skull radiography or Computerized Tomography scan would be used if neonate had neurological symptoms or depressed skull fracture was suspected.

To determine risk factors associated with scalp hematoma, maternal and neonatal medical records were reviewed to collect demographic and clinical data. Baseline maternal characteristics included maternal age, parity, body mass index (BMI), total weight gain (TWG), gestational age and neonatal characteristics included neonatal birth weight, neonatal head circumference and neonatal sex. Information regard to labor and delivery included route of delivery, artificial rupture of membranes, intrapartum oxytocin infusion and duration of second stage of labor. Neonatal outcomes in cases with scalp hematoma were collected.

Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Mean, standard deviation (SD), median, interquartile range (IQR), percentage were used to describe the maternal and neonatal demographic and outcome data. Incidence of neonatal scalp hematoma was presented

as percentage. Chi-square test or Fisher exact test were used to test of association between factors and occurrence of scalp hematoma. Adjusted odds ratios (OR) of the associated factors were determined using logistic regression model adjusted for covariates that found significant association from univariate analysis. P value of less than 0.05 was considered statistically significant.

Results

Between 1st July and 31th October 2016, 1400 neonates delivered in King Chulalongkorn Memorial Hospital. Of all, 462 neonates were excluded: 249 neonates due to implausible data on gestational age; 137 preterm neonates; 29 non-vertex delivered neonates; 13 neonates with major anomalies, 1 neonate with bleeding disorder, 3 neonates born before arrival and missing medical records in 30 neonates. A total of 938 term neonates were included in this study.

Thirty cases were confirmed of having scalp hematoma, yielding an incidence of neonatal scalp hematoma was 3.19% (30/938). Cephalhematoma was found in 14 cases and subgaleal hemorrhage was found in 16 cases. There were 2 neonates having both cephalhematoma and subgaleal hemorrhage and complicated with hypovolemic shock. None was admitted in neonatal intensive care unit or dead.

Table 1. Baseline and clinical characteristics of cases with scalp hematoma and controls.

Variables	Scalp hematoma (n = 30)	Control (n = 908)	p value
Maternal age (year)[a]	29.5 ± 4.8	30.1 ± 6.1	0.59
Gestational age (weeks)[a]	39.0 ± 0.9	38.8 ± 1.0	0.28
Primiparity[b]	26 (86.7%)	480 (52.9%)	< 0.001
Height (cm)[a]	159.6 ± 4.0	158.3 ± 5.7	0.22
BMI (kg/m2)[a]	22.7 ± 5.4	22.2 ± 4.5	0.55
TWG (kg)[a]	14.8 ± 5.3	13.7 ± 5.1	0.25
Duration from membrane rupture to delivery more than 4 hours[b]	17 (56.7%)	277 (30.5%)	0.005
Prolonged second stage of labor[b]	4 (13.3%)	22 (2.4%)	0.007
Artificial rupture of membranes*[b]	19 (67.9%)	206 (41.9%)	0.012
Intrapartum oxytocin infusion*[b]	13 (46.4%)	149 (30.3%)	0.11
Female neonate[b]	14 (46.7%)	459 (50.6%)	0.82
Neonatal birthweight (g)[a]	3180 ± 349	3125 ± 385	0.44
Neonatal head circumference (cm)[a]	33.8 ± 1.2	33.7 ± 1.2	0.65

* Only vaginal delivered women: neonatal scalp hematoma (n=28); control (n=492)

[a] presented as mean ± SD, b presented as number (%)

Maternal and neonatal characteristics and clinical data were shown in Table 1. No difference in maternal age, gestational age, height, BMI and TWG between case and control was found. However, proportions of mothers with primiparity, duration from membranes rupture to delivery more than 4 hours, and prolonged the second stage of labor among cases with hematoma were significantly higher than

those among controls. In women who vaginal delivered, percentages of mothers having artificial rupture of membranes were higher among cases with hematoma when compared with controls, but proportions of women having intrapartum oxytocin infusion were not different. There was no difference in sex, mean birthweights and mean head circumference of neonates between case and control.

Fig. 1. demonstrates the percentages of neonatal scalp hematoma in any route of delivery. Operative obstetrics (vacuum and forceps extraction) were found to have the highest rate (15.38%) of hematoma when compare with other routes of delivery.

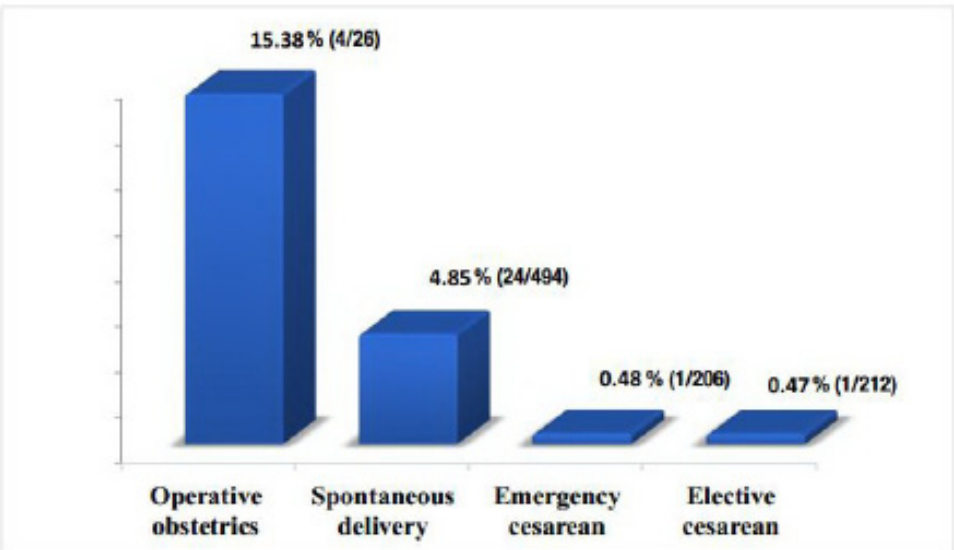

Fig. 1. Percentages of neonatal scalp hematoma by route of delivery.

Table 2. Factors associated with scalp hematoma in total neonates.

Factors	OR	95%CI	AOR*	95%CI
Primiparity	5.79	2.01-16.74	4.86	1.61-14.58
Duration from membrane rupture to delivery more than 4 hours	2.98	1.43-6.22	1.56	0.70-3.48
Prolonged second stage of labor	6.19	1.99-19.27	4.31	1.08-17.25
Route of delivery				
Spontaneous vertex delivery	1		1	
Operative obstetrics	3.56	1.14-11.15	1.32	0.34-5.09
Emergency cesarean delivery	0.09	0.01-0.72	0.08	0.01-0.59
Elective cesarean delivery	0.09	0.01-0.69	0.12	0.02-0.92

* Adjusted for parity, duration from membrane rupture to delivery, second stage of labor, and route of delivery.

Factors associated with scalp hematoma in total neonates were shown in Table 2. From multivariable analysis, factors that significantly increased risk for neonatal scalp hematoma included primiparity

(adjusted OR 4.86, 95%CI 1.61-14.58) and prolonged second stage of labor (adjusted OR 4.31, 95%CI 1.08-17.25). Both emergency and elective cesarean delivery were significantly reduced risk of neonatal scalp hematoma (adjusted OR 0.08, 95%CI 0.01-0.59 and adjusted OR 0.12, 95%CI 0.02-0.92, respectively).

When analysis was done in only neonates who vaginal delivered (Table 3.), the significant risk factors associated with scalp hematoma were primiparity (adjusted OR 3.84, 95%CI 1.26-11.71) and artificial rupture of membranes (adjusted OR 2.93, 95%CI, 1.24-6.97).

Table 3. Factors associated with scalp hematoma in neonates who vaginal delivered.

Factors	OR	95%CI	AOR	95%CI
Primiparity	5.02	1.72-14.67	3.84	1.26-11.71
Artificial rupture of membranes	2.93	1.30-6.61	2.93	1.24-6.97
Duration from membrane rupture to delivery more than 4 hours	2.48	1.14-5.36	2.07	0.88-4.89
Prolonged second stage of labor	5.69	1.74-18.60	3.66	0.81-16.44
Operative obstetrics	3.56	1.14-11.15	1.18	0.28-4.91

* Adjusted for parity, rupture of membranes, duration from membrane rupture to delivery, second stage of labor, and route of delivery.

Discussion

The present study found that 3.19% of term neonates delivered in King Chulalongkorn Memorial Hospital had scalp hematoma. It seem to be higher incidence when compared to previous studies[2,3,9] that reported the injury between 1.28-2.01%. Prospectively surveillance for the hematoma in this study may explain this phenomenon; however, the excess numbers mostly come from the cases with subgaleal hematoma. The incidence of cephalhematoma in this study was 1.49%. It was in the range 1-2% that mostly cited by the literatures[1,4,10]. Although incidence of subgaleal in this study was quite high, the severe cases were found only in 0.21% of neonates.

It is not surprising that neonates vaginal delivered by operative obstetrics had the highest proportion (15.38%) of scalp hematoma while those delivered by elective cesarean section had the lowest proportion (0.47%). Cases indicated for operative obstetrics usually have other risks for scalp injury; in addition, traction force direct to neonatal scalp either by forceps or vacuum cup at contact site may result in rupture of the beneath vessels. Cephalhematoma occurs in 4% of neonates delivered by forceps extractions and the proportion may as high as 26% among neonates delivered by vacuum extractions[10]. However, delivery by operative obstetrics did not significantly associate with neonatal scalp hematoma after multivariable analysis to adjust the covariates was performed.

Regardless route of delivery, the factors significantly increased risk of neonatal scalp hematoma were primiparous women and cases having prolonged second stage of labor. Primiparity was still an important factor that increasing risk of hematoma after analysis was done only in vaginal delivered neonates. The result supported findings from the retrospective case series[7], in which 95% of infants with subgaleal hemorrhage delivered by primiparous mothers.

Similarly to previous reports, cesarean delivery was a protective factor of birth injury[9,11,12]. Interestingly, this study showed that reducing risk of hematoma was found both in neonates delivered by elective cesarean section and those delivered by emergency operation. Although cesarean delivery could reduce risk of a scalp injury, it may increase maternal morbidities and other nonspecific birth trauma[12]. Judicious decision making

on route of delivery should be practiced to approach the favorable maternal and neonatal outcomes.

Among vaginal delivered neonates, artificial rupture of membranes or amniotomy, a common procedure for induction or augmentation of labor, was found to increase risk of neonatal scalp hematoma. An exact mechanism for this event is unknown; however, it may relate to increase of duration from ruptured membranes to delivery or may increase the usage of oxytocin which may result in malposition. It was found that prolonged rupture of membranes (>12 hours) was found in 43% of cases with subgaleal hemorrhage[9]. According to results from a Cochrane review, amniotomy alone did not shorten the duration of spontaneous labor or lower the incidence of cesarean births[13]. The routine practice of artificial rupture of membrane in women with normally labor progression and reassuring fetal status is not needed[14].

The strength of this study was that the scalp injury was prospectively surveillance and diagnosis was validated by experienced neonatologist. However, one of our limitations included the diagnosis of neonatal scalp hematoma was done only by clinical examination. Skull imaging was indicated if there were neurological symptoms and when concomitant depressed skull fracture was suspected, but no neonate in our study was needed.

Conclusion

In conclusion, the incidence of neonatal scalp hematoma in this study was 3.19%. Primiparous women and prolonged second stage of labor were the factors significantly increased risk of neonatal scalp hematoma while cesarean delivery was a protective factor. In vaginal delivered neonates, factors significantly increased risk of neonatal scalp hematoma were primiparity and artificial ruptured of membranes. Proper counseling and judicious decision making on method of delivery should be practiced to reduce the incidence of this birth injury. Further study is warranted to identify intrapartum management protocol that could prevent neonatal scalp injury.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Akangire G, Carter B. Birth injuries in neonates. Pediatr Rev 2016;37:451-62.
2. Sauber-Schatz EK, Markovic N, Weiss HB, Bodnar LM, Wilson JW, Pearlman MD. Descriptive epidemiology of birth trauma in the United States in 2003. Paediatr Perinat Epidemiol 2010;24:116-24.
3. Abedzadeh-Kalahroudi M, Talebian A, Jahangiri M, Mesdaghinia E, Mohammadzadeh M. Incidence of neonatal birth injuries and related factors in Kashan, Iran. Arch Trauma Res 2015;4:e22831.
4. Reichard R. Birth injury of the cranium and central nervous system. Brain Pathol 2008;18:565-70.
5. Zimmermann P, Duppenthaler A. Infected cephalhaematoma in a five-week-old infant - case report and review of the literature. BMC Infect Dis 2016;16:636.
6. Colditz MJ, Lai MM, Cartwright DW, Colditz PB. Subgaleal haemorrhage in the newborn: A call for early diagnosis and aggressive management. J Paediatr Child Health 2015;51:140-6.
7. Swanson AE, Veldman A, Wallace EM, Malhotra A. Subgaleal hemorrhage: risk factors and outcomes. Acta Obstet Gynecol Scand 2012;91:260-3.
8. Carlo WA, Ambalavanan N. Nervous system disorders. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF, editors. Nelson Textbook of Pediatrics, 20th ed. Philadelphia: Elsevier;2016:p 834-44.
9. Linder N, Linder I, Fridman E, Kouadio F, Lubin D, Merlob P, et al. Birth trauma-risk factors and short-term neonatal outcome. J Matern Fetal Neonatal Med 2013;26:1491-5.
10. Doumouchtsis SK, Arulkumaran S. Head trauma after instrumental births. Clin Perinatol 2008;35:69-83.
11. Baskett TF, Allen VM, O'Connell CM, Allen AC. Fetal trauma in term pregnancy. Am J Obstet Gynecol 2007;197:499.e1-7.
12. Moczygemba CK, Paramsothy P, Meikle S, Kourtis AP, Barfield WD, Kuklina E, et al. Route of delivery and neonatal birth trauma. Am J Obstet Gynecol 2010;202:361.e1-6.
13. Smyth RM, Markham C, Dowswell T. Amniotomy for shortening spontaneous labour. Cochrane Database Syst Rev 2013;6: CD006167.
14. Committee on Obstetric Practice. Committee Opinion No. 687: Approaches to limit intervention during labor and birth. Obstet Gynecol 2017;129:e20-8.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 182-189

OBSTETRICS

Acetaminophen/tramadol Rectal Suppository for the Relief of Perineal Pain after Normal Vaginal Delivery: A randomized controlled trial

Chatwadee Pattarasiriwong, M.D.,*,
Densak Pongrojpaw, M.D.,*,
Athita Chanthasenanont, M.D.,*,
Supapen Lertwutwiwat, M.D.,*,
Kornkarn Bhamarapravatana, PhD.,**,
Komsun Suwannarurk, M.D.,*.

** Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat University, PathumThani 12120, Thailand*
*** Department of Preclinical Science, Faculty of Medicine, Thammasat University, PathumThani 12120, Thailand*

ABSTRACT

Objectives: To compare the effectiveness of acetaminophen /tramadol rectal suppository and placebo for pain relief after vaginal delivery

Materials and Methods: Two hundred parturients who delivered vaginally were recruited. Twelve cases were excluded. Cases were randomly divided into two groups; study and control group. Acetaminophen/tramadol was given to the study group and placebo in control group immediately after vaginal delivery. Pain level was measured by visual analogue scale (VAS) at immediate, 6, 12 and 24 hours after delivery. Side effects and additional analgesic medication (acetaminophen) were recorded.

Results: A total of 188 parturients were enrolled. Study and control groups consisted of 98 and 90 cases, respectively. Mean age of cases in this study was 27 years old. Forty percent of cases were nulliparous. All subjects were full term pregnancy with normal body mass index and equally demographic character. Pain score measured by VAS in both groups had no significant difference at all times (0, 6, 12 and 24 hours after delivery). There was no adverse event in this study.

Conclusion: Acetaminophen/tramadol rectal suppository could not relieve perineal pain after normal vaginal delivery when comparing to placebo.

Keywords: acetaminophen/tramadol, pain, vaginal delivery, rectal suppository

Correspondence to: *Densak Pongrojpaw, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat, University, PathumThani 12120, Thailand., Phone: +66-2926-9343, Fax +66-2926-9485, Email: pongrojpaw@gmail.com*

ประสิทธิภาพของยาอะเซตามิโนเฟน/ทรามาดอลเหน็บทางทวารหนักเพื่อลดอาการปวดแผลฝีเย็บในมารดาที่คลอดปกติทางช่องคลอด โดยวิธีการแบบสุ่มและมีการควบคุม

ณัฐวดี ภัทรสิริวงศ์, เด่นศักดิ์ พงศ์โรจน์เผ่า, อธิตา จันทเสนานนท์, สุภาเพ็ญ เลิศวุฒิวิวัฒน์, กรณ์กาญจน์ ภมรประวัติ, คมสันต์ สุวรรณฤกษ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการใช้ยา acetaminophen/tramadol เหน็บทางทวารหนักในมารดาหลังคลอดปกติทางช่องคลอด เพื่อลดอาการปวดแผลฝีเย็บ เปรียบเทียบกับการใช้ยาหลอก*

วัสดุและวิธีการ: *ทำการศึกษาในสตรีตั้งครรภ์ครบกำหนดที่คลอดปกติทางช่องคลอดจำนวน 200 ราย ซึ่งถูกคัดออกเพิ่มเติม 12 ราย ตามข้อบ่งห้ามของการศึกษา นำผู้เข้าร่วมการวิจัยแบ่งโดยสุ่มออกเป็น 2 กลุ่ม กลุ่มที่ทำการศึกษาได้รับยาแก้ปวดอะเซตามิโนเฟน/ทรามาดอล ทางทวารหนักหลังคลอด ประเมินความปวดโดยวัดเป็นคะแนน visual analogue scale เทียบกับกลุ่มที่ได้ยาหลอก ที่เวลาหลังคลอดทันที 6, 12 และ 24 ชั่วโมงหลังคลอด รวมทั้งเก็บข้อมูลถึงผลข้างเคียงของยาที่ใช้ และจำนวนยาแก้ปวด (อะเซตามิโนเฟน) ที่ขอเพิ่มในแต่ละกลุ่ม*

ผลการศึกษา: *จำนวนผู้เข้าร่วมการศึกษาทั้งหมดจำนวน 188 ราย แบ่งเป็นกลุ่มศึกษา 98 ราย และกลุ่มควบคุม 90 ราย อายุเฉลี่ยของผู้เข้าวิจัยคือ 27 ปี เป็นหญิงตั้งครรภ์แรกคิดเป็นร้อยละ 40 ทุกรายที่เข้าร่วมการศึกษาเป็นหญิงที่ตั้งครรภ์ครบกำหนดทั้งหมด และมีข้อมูลประชากรทั่วไปไม่แตกต่างกันในทั้ง 2 กลุ่มทดลอง คะแนนความปวดที่ประเมินที่ช่วงเวลาหลังคลอดทันที 6, 12 และ 24 ชั่วโมง หลังคลอดของทั้งกลุ่มศึกษาและกลุ่มควบคุมไม่มีความแตกต่างอย่างมีนัยสำคัญ ในการศึกษานี้ไม่พบภาวะข้างเคียงที่ไม่พึงประสงค์*

สรุป: *อะเซตามิโนเฟน/ทรามาดอลเหน็บทางทวารหนัก ไม่สามารถระงับความปวดฝีเย็บหลังคลอดปกติทางช่องคลอด เมื่อเทียบกับกลุ่มที่ได้รับยาหลอก*

คำสำคัญ: *อะเซตามิโนเฟน/ทรามาดอล, ความปวด, คลอดปกติทางช่องคลอด, ยาเหน็บทางทวารหนัก*

Introduction

Vaginal delivery is the natural birth process. These days natural birth canal injury is mostly prevented by episiotomy. Episiotomy in vaginal birth causes postpartum pain to the new mother. The depth of episiotomy cut causes various degree of pain. It disturbs the parturient's ambulation, newborn care and lactation[1]. There are many methods for pain relief. Cold packing is commonly used for non-medical postpartum pain relief. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed medicine for pain relief. If the pain is more than usual, opioid-derivatives would then be considered for the patients[1].

The most commonly used medication for pain relief after vaginal delivery is acetaminophen, a non NSAIDs pain reliever. It is a good option for analgesia in nursing mothers because of its safety, but it has less efficacy than NSAIDs[1]. Although NSAIDs are known for their effectiveness in pain control, however, they are excreted in breast milk and might have physiologic effect on the newborns. Gastric irritation is the common effect of NSAIDs in lactating mothers especially in those who were emptying gastric contents during their parturition[2].

Tramadol, a weak opioid agent, has adequate effectiveness for moderate pain control. However, its active metabolite, O-desmethyltramadol, is questioned for its side effect when received by newborn. A serious side effect of tramadol active metabolite is neonatal abstinence syndrome (opioid withdrawal syndrome). It usually occurs in newborns that have prenatal history of maternal opioid usage. This condition is a subject of concern in postpartum women who use opioid during lactation. However, Ilett's work showed that the amount of tramadol excreted via breast milk was very low. No adverse effect was observed in the infant. So, tramadol was acceptable for pain control in postpartum women[3-4]. The use of tramadol was reported in combination with acetaminophen for postoperative pain relief. Synergistic effect of this combination resulted in decreased dosage of opioid derivative[5].

Fixed combination of acetaminophen (325 mg)/tramadol (37.5) (Ultracet®, Janssen-Cilag, USA) was used in this study. The peak blood level of oral form tramadol and acetaminophen are 64.3 and 4.2 ng/mL. Time to peak blood level and half-life are 0.9-1.8 and 2.5-5.1 hours, respectively[6]. For rectal suppository of the tramadol, an absolute bioavailability was 77% (95% confidence interval of 70.8-83.6%)[7]. The peak serum concentration of tramadol rectal administration was 2 to 6 hours and its half-life was 5.7±1.0 hours[7]. For acetaminophen rectal suppository, the study showed that time to peak plasma concentration was 2 hours. The rectal bioavailability was 78% (95% confidence interval of 55-101%). The serum concentration of acetaminophen can be detected for 6 hours[8].

In birthing mother, after perineorrhaphy was done, doctors routinely perform digital rectal examination to make sure that suture material was not perforated in to rectum. We proposed that there was an opportunity to give patients rectal suppository analgesic medication to relief postpartum pain. Rectal administration of tramadol in its commercial suppository preparation gave more rapid therapeutic effect in its oral administration. This finding may be from the absent of first-pass metabolism of tramadol via rectal administration[7].

This study aimed to evaluate the perineal pain control efficacy by fixed combination of acetaminophen (325 mg) and tramadol (37.5 mg) via rectal suppository route in women who underwent episiotomy and perineorrhaphy after vaginal delivery.

Materials and Methods

The study was approved by Human Research Ethics Committee of Thammasat University (COA 064/2559, RCT).

The cases were recruited from healthy singleton parturients who underwent natural vaginal delivery at Thammasat University Hospital (TUH) between February and April 2017. The participants were between 18-40 years old. Inclusion criteria

were gestational age at least 37 completed weeks, and the degree of episiotomy vaginal laceration between 2 and 3. All subjects signed informed consent after counseling. Exclusion criteria were the first and the forth degree of vaginal lacerations, complication of episiotomy wound, any underlying disease of liver or kidney, acetaminophen or tramadol allergic history and patients who refused to take part in this study.

For sample size calculation, we chose Pandleton's study[9] because this research studied about perineal pain control after acetaminophen/tramadol usage. Sample size that calculated from this study was 83.9 cases as that can be rounded up to 85 cases in each group.

Two hundred cases that met the inclusion criteria were recruited in this study. The population was divided into two groups, study and control. The study design was a double-blind randomized controlled trial. Group member selection was performed during childbirth using prepared computer generated number in sealed opaque envelop. The sealed envelope was opened when the cases was in the second stage of labor.

All subjects received 10 mL of 1% lidocaine via local infiltration at perineorrhaphy site after birth immediately before suturing. The study group received combination of acetaminophen/tramadol tablet (325/37.5 mg, Ultracet®, Janssen-Cilag, USA) via rectal suppository. The control group received placebo in the same manner as the study group. Placebo agent was 1000 mg of vitamin C (1000 mg, ACORBIC®, JP natural, USA). It had a similar appearance to acetaminophen/tramadol tablet. The pills were administered immediately after perineorrhaphy completion by physicians who completely performed perineorrhaphy. Routine practice of postpartum care, namely regular vital signs measurement, bleeding observation and administration of oral acetaminophen tablet as requested were provided to the new mothers. Pain score was evaluated at 0, 6, 12 and 24 hours postpartum. Time "0" is start form the completion of episiotomy wound repair. We used visual analogue scale (VAS) for perineal pain. The score was from 0 to 10. The participants were evaluated by structural questionnaire nurse who did not know the type of analgesia. Amount of additional analgesics provided and side effects were recorded.

Data were analyzed using statistical software package SPSS (v 23 SPSS Inc, Chicago, IL, USA.) Continuous data was analyzed by using mean and unpaired t-tests. Chi-square tests were used for categorical data. Level of statistical significant was set at p value < 0.05.

Results

Two hundred parturients were enrolled during the study period. (Fig. 1.) Twelve cases were excluded from the study after exclusion criteria. The study and control group consisted of 98 and 90 cases, respectively. Mean age of both groups were 27 years old. Forty percent of cases were nulliparous. All cases were full term pregnancies with normal body mass index (BMI).

Housewives and office workers both comprised one quarter of the participants (Table 1). Forty percent of cases had monthly income less than 10,000 Baht. One-fifth of cases had higher education than bachelor degree level. Fourteen and eighteen percent of subjects graduated primary school degree in control and study group, respectively. The percentage of diabetes mellitus, hypertension and anemia in both groups had no statistical difference (Table 1). Most cases underwent mediolateral episiotomy. Average newborn weight was three kilograms. Average inner and outer wound lengths were around 7 centimeters. Estimated blood loss was 180 ml and perineorrhaphy time was 30 minutes.

Median of pain score (50th percentile) at 0, 6, 12 and 24 hours after delivery were the same in both groups (4, 3, 3 and 2, respectively) as shown in Table 2. We categorized subjects in to 2 groups of nulliparous and multiparous parturient, but there was no statistical differences. There was no reported of side effect of analgesic used in this study. Eleven

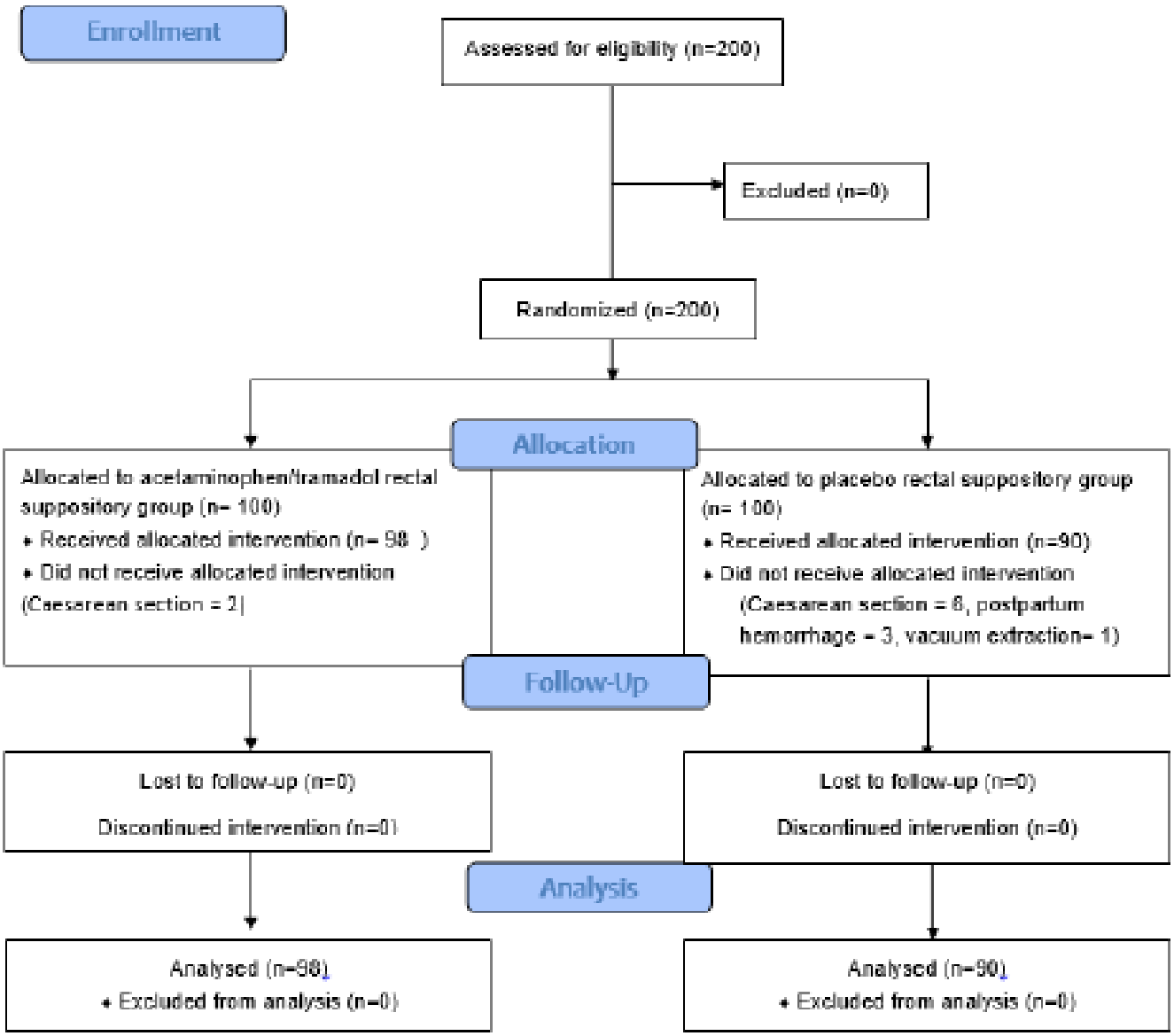

Fig. 1. Participants flow diagram.

patients requested one tablet of 500 mg acetaminophen for additional rescue analgesia (at 6-hours after delivery). Two patients requested two tablets of 500 mg acetaminophen (at 12-hours after delivery).

Discussion

Tramadol is a commonly prescribed drug to treat mild to moderate pain. It is a synthetic opioid of the benzenoid class. O-desmethyltramadol is a metabolite product of tramadol. It gives a better pain relief effect than its precursor[10]. This study was conducted on immediate postpartum women with single application of acetaminophen/tramadol combination to bypass tramadol excretion via breast milk.

During parturition, pregnant subjects were voided of any oral consumption. This protocol was to prevent any gastric aspiration. The Mendelson's syndrome was

Table 1. Demographic data.

Characteristics	group		p value
	control (n=90)	study (n=98)	
Age (years)*	27.5 ± 5.5	27.68 ± 5.6	0.86
Parity#	1 (0-3)	1 (0-3)	0.80
GA (weeks)*	38.04 ± 1.0	38.71 ± 1.0	0.94
BMI (kg/m^2)*	21.8 ± 3.3	21.9 ± 3.2	0.76
ANC risk**			
DM	7 (7.7)	9 (9.2)	0.42
HT	2 (2.2)	2 (2.0)	0.65
Anemia	4 (4.4)	5 (5.1)	0.73
Occupation**			0.07
House wife	23 (25.6)	24 (24.5)	
Own business	14 (15.5)	19 (19.4)	
Employee	46 (51.1)	48 (49.0)	
Government officer	7 (7.8)	7 (7.1)	
Income (Bath/month)**			0.35
≤ 10,000	39 (43.3)	40 (40.8)	
> 10,000	51 (56.7)	58 (59.2)	
Education**			0.70
Primary school	13 (14.5)	18 (18.3)	
Secondary school	31 (34.4)	28 (28.6)	
High school	29 (32.2)	32 (32.7)	
Bachelor or higher	17 (18.9)	20 (20.4)	

* : mean ± standard deviation (SD), # : Median (50th percentile) with range, GA : gestational age, BMI : body mass index, ANC: antenatal care

** n(%), DM: diabetes mellitus, HT: hypertension

a possible serious phenomenon for lung aspiration from gastric content[11]. Rawal et al reported that fixed tablet combination of acetaminophen (325 mg) and tramadol (37.5 mg) given orally had a comparable effect to tramadol 50 mg and less side effect in orthopedic hand surgery cases[12]. The study proved that combination of these two drugs had synergistic efficacy for pain control and allowed the use of smaller dosage of opioid.

The fixed combination of acetaminophen/tramadol was chosen in this investigation for postpartum pain relief. Rectal administration of tramadol in its commercial suppository preparation gave the more rapid therapeutic effect than the oral administration of tramadol, possibly from the absent of first-pass metabolism of tramadol via rectal administration[7].

Rectal administration of oral NSAIDs tablet in immediate postpartum women were reported by a few groups of researchers[13-15]. Achariyapota's and

Table 2. Clinical characteristic of labor and VAS.

Characteristics	group				p value
	control (n=90)		study (n=98)		
Sutured time (min)*	26.9 ± 18.3		31.1 ± 21.2		0.17
Baby birth weight (g)*	3058.7 ± 365.1		3041.9 ± 350.6		0.76
Episiotomy type**					
Median	4 (4.4%)		5 (5.1%)		0.57
Mediolateral	86 (95.6%)		93 (94.9%)		
Wound Length (cm)*					
Inner	3.3 ± 1.2		3.2 ± 1.2		0.51
Outer	3.5 ± 0.9		3.5 ± 0.9		0.84
Degree of laceration**					
Second degree	87 (96.7%)		96 (98.0%)		0.621
Third degree	3 (3.3%)		2 (2.0%)		
EBL (ml)*	183.8 ± 71.9		182.3 ± 81.5		0.89
Pain score (VAS)$^{\int}$					
Immediate	4 (0-10)		4 (0-10)		0.81
6-hours	3 (0-7)		3 (0-7)		0.33
12-hours	3 (0-5)		3 (0-5)		0.85
24-hours	2 (0-8)		2 (0-5)		0.36
Pain Severity**					
	PS < 4	PS ≥ 4	PS < 4	PS ≥ 4	
Immediate	41 (45.6%)	49 (54.4%)	48 (48.9%)	50 (51.1%)	0.64
6-hours	54 (60%)	36 (40%)	56 (57.1%)	42 (42.9%)	0.87
12-hours	72 (80%)	18 (20%)	76 (77.5%)	22 (22.5%)	0.86
24-hours	79 (87.8%)	11 (12.2%)	83 (84.7%)	15 (15.3%)	0.79
Side effect	none		none		-
Additional analgesia (tab)$^{\int}$	0 (0-2)		0 (0-2)		1.00

VAS: Visual analogue scale, min: minutes, * mean ± standard deviation (SD), g : grams, ** number, cm: centimeter, EBL: estimated blood loss, $^{\int}$: Median (50th percentile) with range, PS: pain score

Dodd's studies used diclofenac rectal suppository with a favorable result[13,15]. Oral naproxen was used as rectal suppository in Wilasrusmee's study with a favorable effect[14]. The use of tramadol rectal suppository was reported in Srimaekarat's study. The dosage was 100 mg of tramadol. However, it gave equal effect to placebo[16]. The present study conducted on larger group of subjects than Srimaekarat's study.

In this study, subjects were parturients who gave vaginal delivery. The average VAS of both groups was only 3 from 10 level. Both groups

showed no significant difference of pain score level between acetaminophen/tramadol and placebo groups.

From many studies that mention above, we found that single agent rectal analgesia gave satisfactory results. Hence, we chose a combined medication in this study because we desired the synergistic effect. However, the result was not demonstrated what we expected.

The pain level from normal vaginal delivery was mild to moderate. The limitations of this study were an inadequate dosage of tramadol chosen for the study and low pain level of participating subjects. The next study should be conducted in higher pain level cases, i.e., cesarean section with an improved suppository formulation.

Conclusion

Acetaminophen/tramadol tablet used as rectal suppository was not significantly different in relieving perineal pain after normal vaginal delivery when comparing to placebo. Side effect was not found in this study.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. East CE, Sherburn M, Nagle C, Said J, Forster D. Perineal pain following childbirth: prevalence, effects on postnatal recovery and analgesia usage. Midwifery 2012;28:93-7.
2. Sostres C, Gargallo CJ, Arroyo MT, Lanas A. Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. Best Pract Res Clin Gastroenterol 2010;24:121-32.
3. Ilett KF, Paech MJ, Page-Sharp M, Sy SK, Kristensen JH, Goy R, et al. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. Br J Clin Pharmacol 2008;65:661-6.
4. Hartenstein S, Proquitté H, Bauer S, Bamberg C, Roehr CC. Neonatal abstinence syndrome (NAS) after intrauterine exposure to tramadol. J Perinat Med 2010; 38:695-6.
5. Mattia C, Coluzzi F, Sarzi Puttini P, Viganó R. Paracetamol/Tramadol association: the easy solution for mild-moderate pain. Minerva Med 2008;99:369-90.
6. U.S. Food and Drug Administration [Internet]. 2001 [cited 2017 Oct 10]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21123lbl.pdf
7. Lintz W, Barth H, Osterloh G, Schmidt-Böthelt E. Pharmacokinetics of tramadol and bioavailability of enteral tramadol formulations. 3rd Communication: suppositories. Arzneimittelforschung 1998;48:889-99.
8. Coulthard KP, Nielson HW, Schroder M, Covino A, Matthews NT. Relative bioavailability and plasma paracetamol profiles of Panadol suppositories in children. J Paediatr Child Health 1998;34:425-31.
9. Pendleton J, Costa J, Wludyka P, Carvic DM, Rosser CJ. Combination of oral tramadol, acetaminophen and 1% lidocaine induced periprostatic nerve block for pain control during transrectal ultrasound guide biopsy of the prostate: a prospective, randomized, controlled trial. J Urol 2006;176:1372-5.
10. Bloor M, Paech MJ, Kaye R. Tramadol in pregnancy and lactation. Int J Obstet Anesth 2012;21:163-7.
11. Cunningham FG, Leveno KJ, Bloom SL, Spong CY, Dashe JS, Hoffman BL, et al. Obstetrical analgesia and anesthesia. Williams obstetrics. 24th edition. New York: McGraw Hill Education 2014:504-22.
12. Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. J Pain Res 2011;4:103-10.
13. Achariyapota V, Titapant V. Relieving perineal pain after perineorrhaphy by diclofenac rectal suppositories: a randomized double-blinded placebo controlled trial. J Med Assoc Thai 2008;91:799-804.
14. Wilasrusmee S, Chittachareon A, Jirasiritum S, Srisangchai P. Naproxen suppository for perineal pain after vaginal delivery. Int J Gynaecol Obstet 2008;102: 19-22.
15. Dodd JM, Hedayati H, Pearce E, Hotham N, Crowther CA. Rectal analgesia for the relief of perineal pain after childbirth: a randomised controlled trial of diclofenac suppositories. BJOG 2004;111:1059-64.
16. Srimaekarat T. Tramadol suppository versus placebo for the relief of perineal pain after perineorrhaphy: a randomized controlled trial in Thailand. J Med Assoc Thai 2011;94:17-20.

15. Dodd JM, Hedayati H, Pearce E, Hotham N, Crowther CA. Rectal analgesia for the relief of perineal pain after childbirth: a randomised controlled trial of diclofenac suppositories. BJOG 2004;111:1059-64.
16. Srimaekarat T. Tramadol suppository versus placebo for the relief of perineal pain after perineorrhaphy: a randomized controlled trial in Thailand. J Med Assoc Thai 2011;94:17-20.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 190-197

GYNECOLOGY

Analgesic Effect of Lidocaine Spray during Endometrial Biopsy: A randomized controlled trial

Maneenuch Sripha, M.D.,*,
Chuenkamon Charakorn, M.D.,*,
Navamol Lekskul, M.D.,*,
Arb-aroon Lertkhachonsuk, M.D.,*.

** Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand*

ABSTRACT

Objectives: To investigate the effect of lidocaine spray applied on the cervical surface in pain reduction of patients undergoing endometrial biopsy using the Endosampler instrument.

Materials and Methods: A double-blinded, randomized controlled study was conducted in 100 women undergoing endometrial biopsy. Patients were randomly assigned to receive either lidocaine spray or placebo. Visual analog scale (VAS) was used to assess patients' pain at three points of the procedure (speculum insertion, cannula insertion and after speculum removal). The satisfaction of the procedure was evaluated by patients and doctors using five point Likert scale.

Results: Endometrial biopsy was successfully performed in 100 patients. The median VAS pain score during cannula insertion in the lidocaine group was 5.0 which was lower than 5.5 in the placebo group without statistical significance.

Conclusion: Lidocaine spray application on cervix before endometrial biopsy did not significantly reduce pain in patients who underwent this procedure.

Keywords: endometrial biopsy, lidocaine spray, pain score, randomized controlled trial

Correspondence to: *Navamol Lekskul, M.D., Department of Obstetrics and Gynaecology, Faculty of Medicine Ramathibodi Hospital, Mahidol University; Bangkok 10400, Thailand. Phone: +66-2-2011412, E-mail: navamoll@yahoo.com*

ผลของยาชาชนิดพ่นลิโดเคนในการบรรเทาความเจ็บปวดขณะทำการเก็บเยื่อบุโพรงมดลูก: การศึกษาแบบสุ่ม

มณีนุช ศรีผา, ชื่นกมล ชรากร, นวมลล์ เล็กสกุล, อาบอรุณ เลิศขจรสุข

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาผลของการพ่นยาลิโดเคนที่ปากมดลูกในการลดความเจ็บปวดในผู้ป่วยที่เข้ารับการเก็บเยื่อบุโพรงมดลูกส่งตรวจด้วยเครื่องมือ Endosampler*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่ม โดยเปรียบเทียบกับยาหลอกในผู้ป่วยทั้งหมด 100 ราย ที่เข้ารับการเก็บเยื่อบุโพรงมดลูกส่งตรวจ โดยสุ่มผู้ป่วยออกเป็น 2 กลุ่ม กลุ่มหนึ่งได้รับการพ่นลิโดเคน (50 ราย) อีกกลุ่มหนึ่งได้รับยาหลอก (50 ราย) การประเมินคะแนนความเจ็บปวดทำโดยใช้ visual analog scale ใน 3 ช่วงเวลา ได้แก่ หลังใส่ speculum ขณะสอด cannula และหลังถอด speculum ความพึงพอใจต่อการทำหัตถการประเมินโดยผู้ป่วยและแพทย์ผู้ทำหัตถการโดยใช้ 5 point Likert scale*

ผลการศึกษา: *แพทย์สามารถทำหัตถการได้สำเร็จในผู้ป่วยทั้งหมด 100 ราย ค่ามัธยฐานของคะแนนความเจ็บปวดขณะสอด cannula ในกลุ่ม lidocaine คือ 5 (0-10) ซึ่งต่ำกว่าค่ามัธยฐานของคะแนนความเจ็บปวดขณะสอด cannula ในกลุ่มยาหลอก คือ 5.5 (0-10) แต่ไม่มีมีนัยสำคัญทางสถิติ (p value 0.78)*

สรุป: *การพ่นยาลิโดเคนที่ปากมดลูกก่อนการทำหัตถการเก็บเยื่อบุโพรงมดลูกส่งตรวจ ไม่สามารถลดความเจ็บปวดจากหัตถการดังกล่าวได้อย่างมีนัยสำคัญทางสถิติ*

คำสำคัญ: *การเก็บเยื่อบุโพรงมดลูก, ยาพ่นลิโดเคน, คะแนนความเจ็บปวด, การศึกษาแบบสุ่ม*

Introduction

Endometrial biopsy is one of the most commonly performed procedures in gynecologic outpatient department. Many disorders were indicated for endometrial biopsy such as abnormal uterine bleeding, postmenopausal bleeding, anovulation, and abnormal cervical cytology[1]. Endometrial biopsy is a tool for the diagnosis of endometrial pathology with comparable sensitivity and specificity to fractional curettage[2]. In spite of its benefit, pain during the procedure was evident in previous studies. The pain score during this procedure ranged from 4.6 to 6.9 point out of 10[3-5]. Endometrial biopsy causes pain through cervical traction and dilatation as well as uterine contraction during the suction of endometrium.

Lidocaine spray is an effective local anesthesia used in gynecologic procedures such as loop electrosurgical excision procedure (LEEP)[6], hysterosalpingography[7] and intrauterine device (IUD) insertion[8]. It is also easy to apply and non-invasive. Lidocaine spray causes a reversible blockade of impulse propagation by preventing the inward movement of sodium ions through the nerve membrane. So, it may reduce pain from cervical traction and dilatation but not from uterine contraction. Nowadays, the standard procedure of endometrial biopsy was performed without pain control. This research aimed to study the effect of cervical application of lidocaine spray on pain reduction during endometrial biopsy.

Materials and Methods

This randomized, double-blinded, controlled trial was approved in June 2016 by the Committee on Human Rights Related to Research Involving Human Subjects of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Between June 2016 and June 2017, women with conditions indicated for endometrial biopsy at the gynecologic outpatient department were recruited.

The inclusion criteria were non-pregnant women who were consented for the office-endometrial biopsy. Women with contraindications for lidocaine administrations, such as hypersensitivity to lidocaine or amide type local anesthesia, cardiovascular diseases (heart failure, arrhythmia and bradycardia), severe renal dysfunction, impaired hepatic function and a history of convulsion were excluded from the study. Additional exclusion criteria were uterine anomalies or myoma uteri that distorted the uterine cavity, cervical stenosis, acute cervicitis and pelvic inflammatory disease. Because experience and expectation affected people's pain perception[9], women who had a prior experience with endometrial biopsy or an inability to evaluate pain by visual analog scale (VAS) were also excluded.

After the enrollment, demographic data of the participants was reviewed and analyzed according to the basic categories (e.g, age, underlying disease, number of gravidity, parity and delivery, menstrual history).

One hundred participants were randomly assigned into two groups. Group one received 4 puffs of 10% lidocaine spray (40 mg) applied on the cervix; while, group two received 4 puffs of placebo (normal saline) before endometrial biopsy. Randomization was accomplished by computer-generated block randomization. The randomized numbers were concealed in sealed opaque envelopes which would be opened by a research nurse. The spray bottles used in both groups were covered with the same stickers; consequently, they were identical. The operators, patients and pain evaluator were blinded.

Informed consent was obtained from all participants. Pain evaluation was rated by VAS using a plain 10 centimeter long line labelled on one edge with "worst pain" and another with "no pain". Participants were asked to mark the severity of pain on the line by themselves at 3 different times during the procedure: speculum insertion (VAS1), endosampler cannula insertion (VAS2) and after speculum withdrawal (VAS3). The pain evaluator measured the distance from the "no pain" side to the point which the patient marked in centimeter.

The procedure was standardized and performed by the residents and attending staff of the Department of Obstetrics and Gynaecology, Ramathibodi Hospital, Mahidol University.

After the patients were placed in lithotomy position, the operator inserted a sterile bivalve speculum and asked them to score VAS1 at once. Vagina and cervix were prepped with antiseptic solution; then, 4 puffs of

lidocaine or placebo spray were administered to the cervical surface thoroughly and left for three minutes. Three minute waiting time was the time recommended by the lidocaine spray's manufacturer. Moreover, as reported by Van der Burght M et al, 3 minutes was the duration of mean onset for lidocaine spray application on genital mucosa[10]. The cervical manipulation (with Allis or Tenaculum forceps) was optional. The Endosampler device® with a 3-mm diameter round tip cannula and a self-locking 10-ml syringe was utilized in all participants. While the inserted cannula was advanced to fundus, VAS2 was evaluated before the cannula was connected to the syringe. Endometrial tissue was aspirated systematically from fundus to the internal os throughout the cavity. The instrument and the speculum were removed and any bleeding was ceased. Afterwards, VAS 3 was acquired to represent immediate post procedural pain. The patients were observed for 10 minutes after the procedure. The participants were requested to notify doctors at any time during the procedure if there were any abnormal symptoms and the events would also be recorded. The operators and the participants were requested to complete questionnaires about the satisfaction after the procedure, using 5-point Likert scale.

Sample size calculation was based on the endometrial biopsy-related pain score measured by a 10-cm VAS. Reference values (mean, standard deviation (SD)) were taken from the previous study conducted by Aksoy H, et al[11]. Assuming a 1-cm difference in VAS between the groups as a smallest effect with clinical importance, at least 44 subjects were required in each study group to detect a clinically significant difference between the two groups on a 10-cm VAS scale, with a power of 80% to verify the primary hypothesis and a type I error of 0.05. With the expected 10% dropout rate, we planned to recruit a total of 100 women (up to 50 subjects per study group).

Statistical analysis was performed with STATA software version 14.2. A comparison of the outcomes between the groups which were continuous variables was made by using the Mann-Whitney U test (in a non-parametric distribution) or Student's t test. For categorical variables, the Pearson chi square or Fisher's exact test, as appropriate, was used for comparison. P value less than 0.05 was considered statistically significant.

Result

One hundred participants were recruited in this study (50 in each study group). (Fig. 1.) All of the participants successfully underwent the procedure.

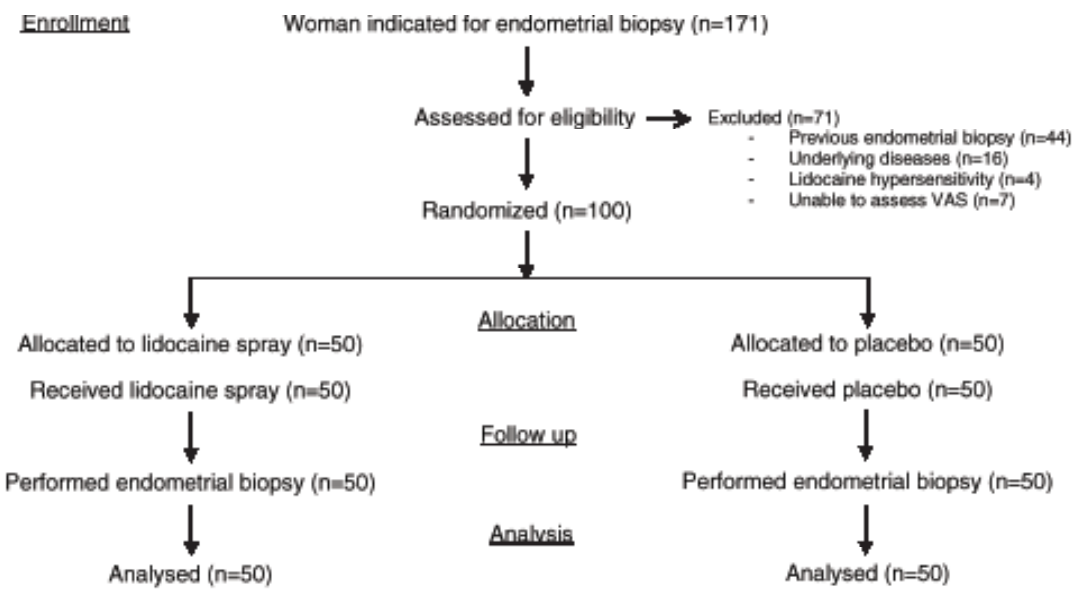

Fig. 1. Study flowchart.

Demographic characteristics of the patients were not statistically significant different between two groups. The most common indication for endometrial biopsy was menometrorrhagia. The use of instruments for cervical manipulation was comparable between the two groups. The mean operative time (from cannula insertion to removal of the speculum) was 3 minutes. No participant demonstrated any adverse reaction or complication in this study. The demographic data and baseline characteristics were demonstrated in Table. 1.

Table 2 demonstrates the VAS at 3 points of the procedure in the lidocaine and the placebo group. The median baseline pain score assessed by VAS (speculum insertion) was 0.5 (0-8) in the treatment group and 0.3 (0-6.2) in the placebo group. The median pain score during cannula insertion was 5.0 (0-10) in the treatment group and 5.5 (0-10) in the control group (p = 0.78). The pain score in the lidocaine group was lower than the placebo group without statistical significance. The median pain score after the procedure (speculum withdrawal) was 2.9 (0-9.7) in the treatment group and 2.3 (0-10) in the control group. The mean patient satisfaction score was 4 ± 0.89 in the treatment group and 4 ± 0.71 in the control group. The mean satisfaction score of the doctors was 4 ± 0.77 in the treatment group and 4 ± 0.76 in the control group (Table 3).

Table 1. Demographic data.

Demographic data	Lidocaine N=50	Placebo N=50	p value
Age (years) (mean±SD)	49.32 ± 9.89	47.42 ± 10.67	0.35
Parity (median (range))	2 (0-4)	1 (0-3)	0.14
Nulliparity	12 (24)	18 (36)	0.27
Parous	38 (76)	32 (64)	
Previous vaginal delivery	33 (66)	26 (52)	0.22
Menopausal status			
Menopause	16 (32)	13 (26)	0.66
Premenopause	34 (68)	37 (74)	
Endometrial thickness (cms) (median (range))	0.96 (0.36-3)	1 (0.41-2.1)	0.80
Cervical manipulation			
No	29 (58)	35 (70)	0.29
Yes	21 (42)	15 (30)	
Cannulation attempt (median (range))	1 (1-5)	1 (1-5)	0.24
Operation time (min) (median (range))	3 (0.5-15)	3 (0.5-20)	0.39
Operator			
Residents	41 (82)	39 (78)	0.80
Attending staff	9 (18)	11 (22)	
Indication for endometrial biopsy			
Postmenopausal bleeding	15 (30)	12 (24)	0.24
Menometrorrhagia	35 (70)	35 (70)	
Others	0 (0)	3 (6)	

Table 2. Pain score at different stage of procedure.

Pain score* (0-10)	Lidocaine group N=50	Placebo group N=50	p value
VAS before insert cannula	0.5 (0-8)	0.3 (0-6.2)	0.44
VAS insert cannula	5.0 (0-10)	5.5 (0-10)	0.78
VAS after procedure	2.9 (0-9.7)	2.3 (0-10)	0.83
VAS difference (Insert cannula and before insertion)	3.5 (0-10)	3.6 (0-10)	0.73

* data are presented in median (range) (cm.)

Table 3. Satisfaction of patients and doctors.

Satisfaction score* (0-5)	Lidocaine group N=50	Placebo group N=50	p value
Patient	4 ± 0.89	4 ± 0.71	0.80
Doctor	4 ± 0.77	4 ± 0.76	0.43

Table 4. Factors associated with pain perception and pain score during the procedure (VAS2).

Factors	N (%)		VAS2 (median (range))		p value
	Lidocaine group N=50	Placebo group N=50	Lidocaine group N=50	Placebo group N=50	
Parity					0.57
Nulliparity	12 (24)	18 (36)	6.6 (0.9-10)	5.5 (0-10)	
Parous	38 (76)	32 (64)	3.8 (0-10)	5.9 (0-9.9)	
Previous vaginal delivery					0.04
Yes	33 (66)	26 (52)	3.5 (0-10)	4.4 (0-9.8)	
No	17 (34)	24 (48)	6.2 (0.9-10)	6.5 (0-10)	
Menopausal status					0.24
Premenopause	34 (68)	37 (74)	3.6 (0.4-10)	5.5 (0-10)	
Menopause	16 (32)	13 (26)	6.0 (0-9.5)	6.5(0.2-9.5)	
Cervix manipulation					0.24
Yes	21 (42)	15 (30)	6.8 (0.9-10)	3.6 (0-9.8)	
No	29 (58)	35 (70)	3.8 (0.4-10)	5.6 (0-10)	
Operator					0.24
Residents	41 (82)	39 (78)	3.9 (0-10)	5.5 (0-9.9)	
Attending staff	9 (18)	11 (22)	6.8 (1.2-10)	6.6 (0.3-10)	

None of the patients requested for the analgesia during the 10 minutes observation period after the procedure and no analgesia was given. Factors relating to pain during endometrial biopsy were demonstrated in Table 4. Operator, cervical manipulation and patient's parity did not significantly affect pain score during the procedure. The history of vaginal delivery decreased the procedural pain. From demographic data, the number of nulliparous was not significantly different between the lidocaine and placebo groups.

Discussion

Endometrial biopsy is a procedure frequently performed in the gynecologic outpatient department for the diagnosis of abnormal uterine bleeding. Even though the procedure is convenient to perform without the need for hospitalization or anesthesia, the pain during the operation is unavoidable. The mean pain score measured by VAS in the previous studies of endometrial sampling without pain control ranged from 4.6-6.9 cm[3-5]. Various methods of pain management have been studied, such as premedication with misoprostol[12], non-steroidal anti-inflammatory drugs (NSAIDs)[13], and paracervical nerve block[14]. The adverse effects from those analgesia were also focused. Misoprostol ingestion prior to the endometrial biopsy did not reduce discomfort and was associated with more side effects of nausea, diarrhea, cramping, abdominal pain, and vaginal bleeding[12]. Naproxen significantly decreased pain score during the endometrial biopsy but the adverse effect of nausea was noticed in the study of Somchit et al[13]. The paracervical nerve block reduced pain originating from cervical dilatation in the endometrial biopsy but provoked the adverse effect of vasovagal syncope[14].

The spray form of lidocaine is the effective method for pain control in gynecologic procedure such as IUD insertion[8], hysterosalpingography[7], LEEP[6] and endometrial biopsy[11]. In the current study, the authors conducted a randomized controlled trial to study the effect of topical lidocaine spray to reduce pain during endometrial biopsy using Endosampler instrument.

The result from the present study proclaimed no statistically significant difference in the VAS pain score, 5.0 in the lidocaine group, comparing with 5.5 in the placebo group. However, the pain scores in our study were more than those reported in Aksoy's study[11], 3.51 in the lidocaine group and 5.11 in the placebo group. This discrepancy may be a consequence of the difference in population. There was a higher number of nulliparous women comprised in this study, 30% as compared to 3.3% in Aksoy's. The other possibility was the dissimilarity in the instruments. We used Endosampler; whilst, the previous study used Karman cannula. Women's pain perception was additionally affected by their cultures, experiences and tolerances which were difficult to standardize.

The strength of the present study was a randomized study conducted with concealment. The operators, patients and pain assessor were blinded regarding the group allocation. The technique of endometrial biopsy was standardized among operators. The protocol of pain evaluation was comprehensively described. The patient evaluated pain by themselves concurrently at the time of the pain perception which helped eliminate the recall bias of data. Furthermore, no adverse effect was reported in both study groups.

The limitation of the present study was a confined sample size to show significantly different pain between two groups. Besides, the procedural pain arising in the uterine cavity and from the contraction may not be managed by the application of lidocaine spray on the cervix. From the advantage of simplicity and safety of the lidocaine spray application, it might still be considered as an adjuvant pain control with other methods. Further studies with a higher number of participants and different dosage of lidocaine spray are needed to establish the potential effect of the lidocaine spray for pain control during endometrial biopsy.

Conclusion

Lidocaine spray application on the cervix before endometrial biopsy did not significantly reduce pain in

patients who underwent this procedure.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Committee on Practice Bulletins-Gynecology. Practice 1. Committee on Practice Bulletins-Gynecology. Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. Obstet Gynecol 2012;120:197-206.
2. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer 2000;89:1765-72.
3. Van den Bosch T, Verguts J, Daemen A, Gevaert O, Domali E, Claerhout F, et al. Pain experienced during transvaginal ultrasound, saline contrast sonohysterography, hysteroscopy and office sampling: a comparative study. Ultrasound Obstet Gynecol 2008;31:346-51.
4. Leclair CM, Zia JK, Doom CM, Morgan TK, Edelman AB. Pain experienced using two different methods of endometrial biopsy: a randomized controlled trial. Obstet Gynecol 2011;117:636-41.
5. Khalid AS, Burke C. A randomised trial of Medgyn Endosampler® vs Endocurette® in an outpatient hysteroscopy clinic setting. Gynecol Surg 2014;11:179–18.
6. Vanichtantikul A, Charoenkwan K. Lidocaine spray compared with submucosal injection for reducing pain during loop electrosurgical excision procedure: a randomized controlled trial. Obstet Gynecol 2013;122:553-7.
7. Karasahin E, Alanbay I, Keskin U, Gezginc K, Baser I. Lidocaine 10% spray reduces pain during hysterosalpingography: a randomized controlled trial. J Obstet Gynaecol Res 2009;35:354-8.
8. Aksoy H, Aksoy U, Ozyurt S, Acmaz G, Babayigit M. Lidocaine 10% spray to the cervix reduces pain during intrauterine device insertion: a double-blind randomised controlled trial. J Fam Plann Reprod Health Care 2016;42:83-7.
9 Swieboda P, Filip R, Prystupa A, Drozd M. Assessment of pain: types, mechanism and treatment. Ann Agric Environ Med 2013; Special Issue 1:2–7.
10 Van der Burght M, Schonemann NK, Laursen JK, Arendt-Nielson L, Bjerring P. Onset and duration of hypoalgesia following application of lidocaine spray on the genital mucosa. Acta Obstet Gynecol Scand 1994;73:809–11.
11. Aksoy H, Aksoy U, Ozyurt S, Acmaz G, Babayigit MA, Yucel B, et al. Effect of lidocaine spray in pain management during office-based endometrial sampling: A randomised placebo-controlled trial. J Obstet Gynaecol 2016;36:246-50.
12. Crane JM, Craig C, Dawson L, O'Grady T, Bartellas E, Hutchens D. Randomized trial of oral misoprostol before endometrial biopsy. J Obstet Gynaecol Can 2009;31:1054-9.
13. Somchit W, Lertkhachonsuk AA, Vallipakorn SA. Naproxen for pain relief during endometrial biopsy: A Randomized Controlled Trial. J Med Assoc Thai 2015;98:631-5.
14. Cengiz H, Dagdeviren H, Kaya C, Yesil A, Caypinar SS. Comparing the efficacy of intrauterine lidocaine and paracervical block in decreasing the pain associated with endometrial biopsy: a randomised trial. Arch Gynecol Obstet 2014;289:609-14.

Thai Journal of Obstetrics and Gynaecology
July 2018, Vol. 26, No. 3, pp. 198-204

GYNECOLOGY

Sublingual Misoprostol for Unsatisfactory Colposcopic Finding: A randomized controlled trial

Sasitorn Wongart, M.D.*,
Maleechat Sripipattanakul, M.D.*,
Thumwadee Tangsiriwatthana, M.D.*,
Sukanda Mahaweerawat, M.D.*.

** Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen 40000, Thailand*

ABSTRACT

Objectives: To assess the effectiveness of 200 µg sublingual misoprostol for converting an unsatisfactory to satisfactory colposcopic finding.

Materials and Methods: Forty-two participants with abnormal cervical cytology and unsatisfactory colposcopic finding who underwent colposcopy between September 2016 and June 2017 were randomized into two groups; either misoprostol or placebo given sublingually. Second colposcopy was performed 2 hours later, and the conversion rate of unsatisfactory to satisfactory colposcopic finding of both groups was analyzed.

Results: Baseline characteristics were similar between two groups. Conversion rate of unsatisfactory to satisfactory colposcopic finding in participants who received sublingual misoprostol was statistically significant higher than placebo group (80.9% vs 38.1%, p = 0.011, relative risk = 2.1, 95% confidence interval 1.18-3.80). There was no significant difference in adverse effect between groups.

Conclusion: Two hundred micrograms of sublingual misoprostol, 2 hours before performing colposcopy can convert an unsatisfactory finding to a satisfactory one.

Keywords: unsatisfactory colposcopy, abnormal pap smear, sublingual misoprostol

Correspondence to: *Sasitorn Wongart, M.D., Department of Obstetrics and Gynecology, Khon Kaen Hospital, Khon Kaen, 40000, Thailand, Phone: (043)232555, E-mail: Sasitorn.wongart@gmail.com*

การใช้ยา misoprostol อมใต้ลิ้นกับยาหลอกในผู้ป่วยที่มีผลตรวจกล้องส่องขยายทางช่องคลอดเป็น unsatisfactory

ศศิธร วงศ์อาจ, มาลีชาติ ศรีพิพัฒนะกุล, ทุมวดี ตั้งศิริวัฒนา, สุกานดา มหาวีรวัฒน์

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของยา misoprostol 200 ไมโครกรัม อมใต้ลิ้นในการเปลี่ยนแปลงผลตรวจกล้องส่องขยายทางช่องคลอดจาก unsatisfactory เป็น satisfactory

วัสดุและวิธีการศึกษา: ผู้เข้าร่วมวิจัยจำนวน 42 คน ที่ผลตรวจมะเร็งปากมดลูกผิดปกติและผลตรวจกล้องส่องขยายทางช่องคลอดเป็น unsatisfactory ที่เข้ามาตรวจที่ colposcopic clinic รพ.ขอนแก่น ในช่วงเดือนกันยายน 2559 ถึง มิถุนายน 2560 ได้รับการสุ่ม เป็น 2 กลุ่ม คือ กลุ่มที่ได้รับยา misoprostol อมใต้ลิ้น และกลุ่มที่ได้รับยาหลอกอมใต้ลิ้นเป็นเวลา 2 ชม. โดยเปรียบเทียบความสามารถในการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory

ผลการวิจัย: ผู้เข้าร่วมวิจัยทั้งสองกลุ่มมีลักษณะพื้นฐานไม่แตกต่างกัน ผู้เข้าร่วมวิจัยในกลุ่มที่ได้รับ misoprostol มีอัตราการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory มากกว่ากลุ่มที่ได้ยาหลอกอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 80.9 กับร้อยละ 38.1, p = 0.011, RR = 2.1, 95% CI 1.18-3.80) โดยไม่พบผลข้างเคียงที่รุนแรง

สรุป: ยา misoprostol 200 ไมโครกรัม อมใต้ลิ้นเป็นเวลา 2 ชม. ก่อนส่องกล้องขยายทางช่องคลอด มีความสามารถในการเปลี่ยนปากมดลูกจาก unsatisfactory เป็น satisfactory ในผู้เข้าร่วมวิจัยที่ตรวจพบความผิดปกติของปากมดลูกได้

คำสำคัญ: ผลส่องกล้องขยายทางช่องคลอดไม่เป็นที่น่าพอใจ, ผลตรวจมะเร็งปากมดลูกผิดปกติ, ยาไมโซพรอสตอลอมใต้ลิ้น

Introduction

Cervical cancer is the most common gynecologic cancer in Thailand[1]. Cervical cancer has a long pre-invasive period which can be detected by conventional Pap smear or liquid-based cytology[2]. An abnormal cytology must be further diagnosed using colposcopy[3]. An unsatisfactory colposcopic finding is defined as a transformation zone, such that the location of the common area of an abnormal lesion, is not be completely visualized[3-6]. The incidence of unsatisfactory colposcopy is between 10-15%. Invasive diagnostic procedures such as loop electrosurgical excision and/or endocervical curettage can be performed but this increases complications and morbidity[6].

Misoprostol is a prostaglandin E1 that is used to soften the cervix of non-pregnant women[7-8]. Previous studies reported the effectiveness of vaginal misoprostol in converting an unsatisfactory to a satisfactory colposcopic finding[9-12]; however, vaginal misoprostol took 4-6 hours for drug administration before performing the colposcopy[9,12]. The long waiting time is inconvenient and impractical in an outpatient setting. Sublingual misoprostol 1 hour prior to vacuum aspiration was significantly more effective in softening the cervix than the vaginal route[13]. There has been no study about the effectiveness of sublingual misoprostol for converting unsatisfactory to satisfactory colposcopic findings. This study was thus conducted to assess the efficacy of sublingual misoprostol to convert an unsatisfactory to a satisfactory colposcopic finding.

Materials and Methods

A double blind, randomized, controlled trial was conducted at Khon Kaen Hospital, Thailand between September 2016 and June 2017. This study was approved by the Khon Kaen Hospital Institutional Review Board for Human Research. All participants were informed about the study and signed the informed consent form before enrollment.

We included participants 18 years or over with an abnormal Pap smear, equivocal types (i.e., Atypical Squamous cell of Undetermined Significance, ASCUS; Atypical Glandular cell, (not otherwise specified, NOS), Low Grade Squamous Intraepithelial Lesion, LSIL) with unsatisfactory colposcopic finding and no history of previous hysterectomy. We excluded participants with a history of hypersensitivity to prostaglandins, having gross cervical mass, having had a prior surgical procedure of the cervix (i.e. conization or LEEP).

The unsatisfactory colposcopic finding defined as a transformation zone could not be completely visualized. An unsatisfactory colposcopy could be found among women with a premenopausal or postmenopausal status; thus both conditions were included in the study, and balanced by randomization.

Eligible participants were randomized by computer generated block of four into two groups; misoprostol and placebo. The random numbers were put into sequentially sealed opaque envelopes. Participants in the study group received 1 tablet of 200 µg sublingual misoprostol and the control group received 1 tablet of sublingual placebo. The second colposcopy was performed 2 hours after drug administration after which the conversion rate was recorded. Side effects such as fever, nausea and vomiting, abdominal pain, diarrhea, and shivering were recorded 4 hours after drug administration. The primary outcome was the conversion rate from an unsatisfactory to a satisfactory colposcopic finding. The secondary outcomes were adverse effects (i.e., fever, nausea, vomiting, abdominal pain, diarrhea, and shivering).

The sample size was calculated based on an error value of 0.05 and a power of 80%. We used the proportion from the pilot study to calculate the sample size (viz., a conversion rate of 80% and 30% in the intervention and control group, respectively). The total number of participants was 42 (21 in each group).

Statistical analysis

Categorical variables were analyzed using the Chi-square test or Fisher's exact test. Continuous

variables were analyzed using the Student t-test or the Mann-Whitney U-test depending on the data distribution. The primary outcome was presented as the relative risk with a 95% confidence interval. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using STATA version 13.

Results

Forty-two participants who had an unsatisfactory colposcopy (i.e., the transformation zone could not be completely visualized) were randomly assigned into two groups (21 per group) (Fig. 1). Demographic data including age, body mass index (BMI), underlying diseases, history of drug allergy, menopausal status, parity, anti-HIV test, number of partner were similar in both groups (Table 1). There have more cases of postmenopausal women than premonapausal women in both groups (15 of 21 in each group). The cervical cytology was not different between groups (Table 2). The conversion rate of unsatisfactory to satisfactory colposcopic finding in the misoprostol group was significantly higher than in the placebo group (80.9% vs. 38.1%, and the relative risk (RR) was 2.1, (95% CI 1.18-3.80), p = 0.011). (Table 3)

The adverse effect 'abdominal pain' was found in 3 of 21 (14.29%) and 2 of 21 (9.52%) in the study and control group, respectively. Other adverse effects were also found such as 1 bleeding per cervical os and 1 palmar rash in study group. There were no other serious adverse effects detected. (Table 4)

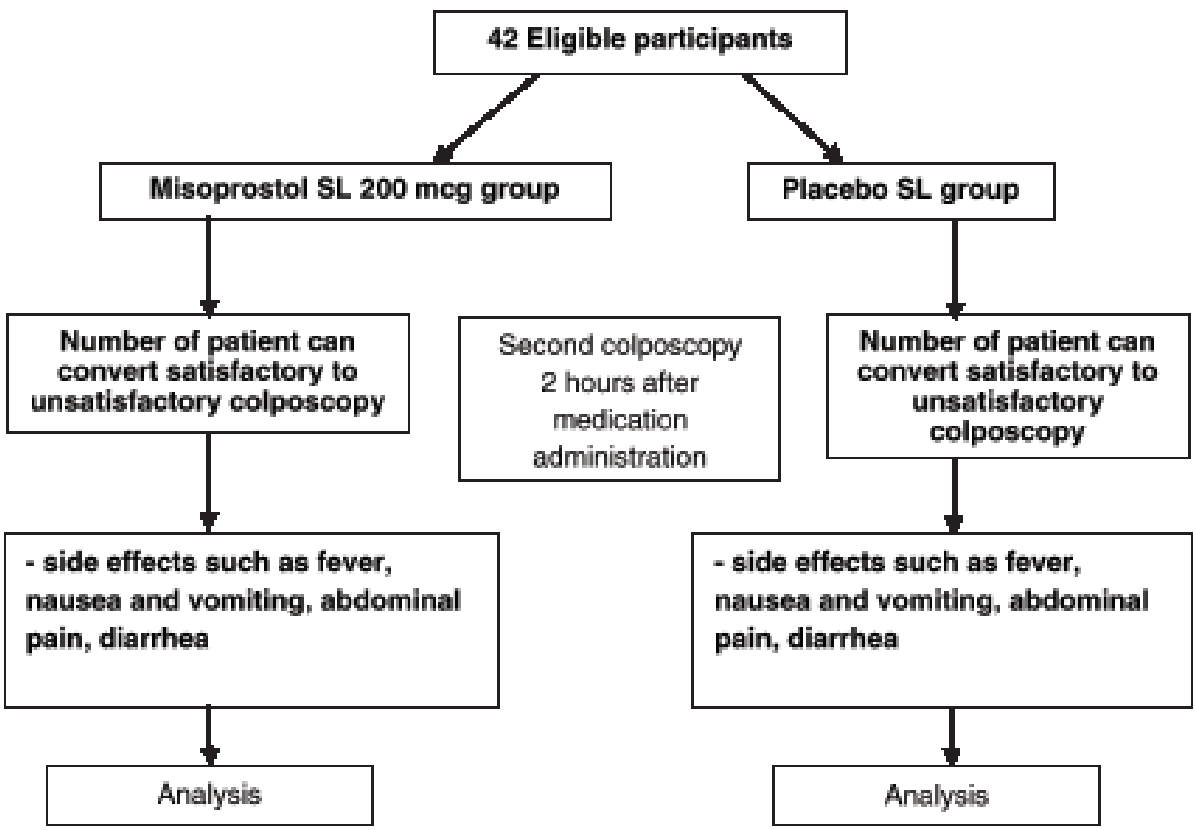

Fig. 1. Participants flow diagram.
(SL, sublingual; mcg, microgram)

Table 1. Demographic data of participants.

Characteristic	Study group (misoprostol) (n=21)	Control group (placebo) (n=21)	p value
Age, years (mean ± SD)	42.9 ± 11.5	36.7 ± 11.2	0.10
BMI, kg/m^2 (mean ± SD)	23.5 ± 3.7	22.8 ± 4.4	0.49
Underlying disease, n (%)	7 (33.3)	4 (19.1)	0.48
Drug allergy, n (%)	1 (4.7)	1 (4.7)	1.00
Parity			
- Multiparous (vaginal birth), n (%)	19 (90.5)	13 (61.9)	0.58
Anti HIV, n (%)			
Menopause status	4 (19.1)	4 (19.1)	0.58
- Postmenopausal age, n (%)	15 (71.4)	15 (71.4)	1.00
Multiple partner, n (%)	13 (61.9)	14 (66.7)	0.57

BMI : Body mass index; SD : Standard deviation; HIV : Human immunodeficiency virus; n : number of patients

Table 2. Cervical cytology.

Cervical cytology	Study group (misoprostol) (n = 21)	Control group (placebo) (n = 21)	p value
ASCUS	8	11	0.354
LSIL	13	9	
AGC NOS	0	1	

ASCUS : Atypical squamous cells of undetermined significance; LSIL : Low grade squamous intraepithelial lesion;
AGC NOS : Atypical glandular cells, not otherwise specified; n : number of patients

Table 3. Primary outcomes.

Colposcopic examination	Study group (misoprostol) (n=21)	Control group (placebo) (n=21)	RR	95%CI	p value
Satisfactory, n (%)	17 (80.95)	8 (38.10)	2.1	1.18-3.80	0.011
Unsatisfactory, n (%)	4 (19.05)	13(61.90)			

RR : Relative risk; 95%CI : Confidence interval; n : number of patients

Table 4. Secondary outcomes.

Side effect	Study group (n = 21)	Control group (n = 21)	p value
Fever n,%	0	0	1.000
N/V n,%	0	0	
Abdominal pain n,%	3 (14.29)	2 (9.52)	
Diarrhea n,%	0	0	
Chills and shivering n,%	0	0	
Bleeding per cervical os n,%	1 (4.76)	0	
Palmar rash n,%	1 (4.76)	0	

N/V : nausea and vomiting; n : number of patients

Discussion

Our findings support the hypothesis that 200 µg misoprostol sublingual 2 hours prior to colposcopy was able to convert an unsatisfactory to a satisfactory colposcopic finding. The conversion rate of the misoprostol group was 80.9% compared to 38.1% in the placebo group (p = 0.011, RR 2.1, 95%CI 1.18-3.80). This finding was consistent with Aggarwal et al[9], whose study was different from ours in dosage and route of administration (i.e., they used 400 µg misoprostol). By comparison, Tungmunsakulchai et al[12], used a lower dose of 200 µg misoprostol, which had a shorter waiting time (4 hours) before the next colposcopy. Tungmunsakulchai et al[12], found that the effectiveness was not significantly different from the findings of Aggarwal et al. and it had fewer adverse effects.

In our study, a dose of 200 µg of misoprostol 2 hours before a second colposcopy was chosen because Aronsson et al[14], showed that sublingual misoprostol was rapidly absorbed and peak plasma levels were reached significantly faster compared with the vaginal route.

Regardless menopausal status, current study had higher incidence of postmenopausal women in both group than Tungmunsakulchai et al[12], however the result was no difference.

Although a previous study showed greater adverse effects from the sublingual route of misoprostol than the vaginal route, we did not find any serious or life-threatening adverse effects. Notwithstanding, a small number of non-serious adverse effects (i.e., abdominal pain and vaginal bleeding) were documented after sublingual administration of misoprostol in both groups[9,14].

Although the second colposcopy was performed 2 hours after drug administration, which is shorter than in previous studies, the conversion rate of unsatisfactory to satisfactory colposcopic finding was still appreciable higher[9,12].

The strength of the present study was that it was a randomized controlled trial and there were no dropouts. Sublingual misoprostol 200 µg taken 2 hours before coloscopy was a useful preparation for converting an unsatisfactory to a satisfactory colposcopic finding in the outpatient setting and could thus reduce morbidity from overtreatment. Among post-menopausal participants, the morphology of cervical epithelium was more difficult to convert to a satisfactory colposcopic finding than among pre-menopausal women. Further study is needed to elucidate the mechanism among post-menopausal women.

Conclusion

Two hundred microgram sublingual misoprostol, 2 hours before performing colposcopy can convert an unsatisfactory to a satisfactory cloposcopic finding.

Acknowledgements

The authors thank (a) the patients for their participation (b) Khon Kaen Hospital for its support, and (c) Mr. Bryan Roderick Hamman for assistance with the English-language presentation of the manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

References

1. Ferley J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Cancer Base No. 5, version 2.0. Lyon: IARC Press 2005.
2. Sankarnarayan R, Budukh A, Rajkumar R. Effective screening programmes for cervical cancer in low and middle income developing countries. Bull World Health Organ 2001;79:954-62.
3. Apgar BS, Brotzman GL, Splitzer M. Colposcopy, principles and practice: An integrated textbook and atlas. 1st ed. Philadelphia: W.B. Saunders Company 2002. p115-82.
4. Rome RM, Chanen W, Ostor AG. Preclinical cancer of the cervix: diagnostic pitfalls. Gynecol Oncol 1983;22:302-20.
5. Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: A beginners' manual. International agency for research on cancer. Lyon: IARC Press 2003;89-94.
6. Martin-Hirsch PP, Paraskevaidis E, Bryant A, Dickinson HO, Keep SL. Surgery for cervical intraepithelial neoplasia. Cochrane Database Syst Rev 2010; 16;(6):CD001318. doi: 10.1002/14651858.CD001318. pub 2.
7. Preutthipan S, Herabutya Y. A randomized controlled trial of vaginal misoprostol for cervical priming before hysteroscopy. Obstet Gynecol 1999;94:427-30.
8. Preutthipan S, Herabutya Y. A randomized comparison of vaginal women before operative hysteroscopy. Fertil Steril 2006;86:990-4.
9. Aggarwal R, Suneja A, Agarwal N, Mishra K. Role of misoprostol in overcoming an unsatisfactory colposcopy: a randomized double-blind placebo-controlled clinical trial. Gynecol Obstet Invest 2006;62:115-20.
10. Thanapprapasr D, Wilailak S, Israngura Na, Ayudhya N, Lertkhachonsuk A, Likittanasombut P, et al. Can vaginal misoprostol effectively increase rate of a satisfactory colposcopy: a randomized double-blind placebo-controlled trial. Jpn J Clini Oncol 2010;40:203-7.
11. Makkar B, Batra S, Gandhi G, Zutshi V, Goswami D. Vaginal misoprostol versus vaginal estradiol in overcoming unsatisfactory colposcopy. Gynecol Obstet Invest 2014;77:176–9.
12. Tungmunsakulchai R, Sripipattanakul M. Misoprostol versus placebo for unsatisfactory colposcopic finding: a randomized controlled trial. Thai J Obstet Gynaecol 2010;18:134-8.
13. Saav I, Kallner H K, Fiala C, Danielsson K G. Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 hour prior to surgical abortion: a double blinded randomized controlled trial. Human Reproduction 2015;30:1314-22.
14. Aronsson A, Fiala C, Stephansson O, Granath F, Schweer H, Gemzell-Danielsson K. Pharmacokinetic profiles up to 12 h after administration of vaginal, sublingual and slow-release oral misoprostol. Hum Reprod 2007;22:1912-8.
15. Aronsson A, Helstrom L, Gemzell-Danielsson K. Sublingual compared with oral misoprostol for cervical dilataion prior to vacuum aspiration: a randomized comparison. Contraception 2004;69:165-9.