VOLUME 43 ISSUE 2
MARCH-APRIL

THE CLINICAL ACADEMIA

We are indexed in
Group I of the Thai journal citation index (TCI)
ASEAN citation index (ACI)

www.kkh.go.th/tca
PRINTED IN THE USA
ISSN:2465-4027


I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla

the clinical academia

Aim and Scope

Our journal is an opened access international journal devoted to peer-reviewed contributions dealing with clinical medicine and medical education from experimental to clinical aspects. Our journal publishes only high quality research, review and other types of original articles, technical and clinical reports every two months. Reviews of various global and Asian aspects will be solicited. Innovation or epidemiological aspects as well as health system research will be addressed. Rigorous systematic review and neglected tropical diseases are our priority

We.....

- are in ASEAN Citation Index (ACI)
- are in Group I of Thai Journal Citation Index (TCI)
- are open access peer-reviewed journal
- 100% check for plagiarism using "turnitin"
- are a registered member of Committee on Publication Ethics (COPE)
- publish only English articles
- publish every 2 months
- request all submitted manuscripts to be provided to with documents regarding ethical approval
- request all original database to be submitted with every manuscript
- request all submitted randomized controlled trial study to be presented with Clinical Trial Registry Number
- Use Digital Object Identifier System (DOI) for all published documents since 2017

the clinical academia

OWNED BY
The Medical Advancement Foundation

Under the Patronage of
Khon Kaen Medical Education Center
Khon Kaen Hospital
Thai Ministry of Public Health

message from the editor

Welcome. This is our second issue of this year, our 43 cherished years. We still have many interesting articles as usual. In this issue, you will learn about the delayed time in the hospital and the outcomes of treatment in those with acute stroke. Our first article will tell you that some fragments of time are so precious. The second article proved the hypothesis that showed the association between sites of cord insertion and preeclampsia in pregnant mothers. A systematic review from the medical students is also what you can expect from us. You will know more about the two options for treating plantar warts which are nicely presented in the third article. And the last is the rare presentation of chromoblastomycosis in our case report section. So far, enjoy!

Thammasorn Jeeraaumponwat, M.D., Ph.D.
Editor-in-Chief of The Clinical Academia

submission

Please visit

www.kkh.go.th/tca

For online submission

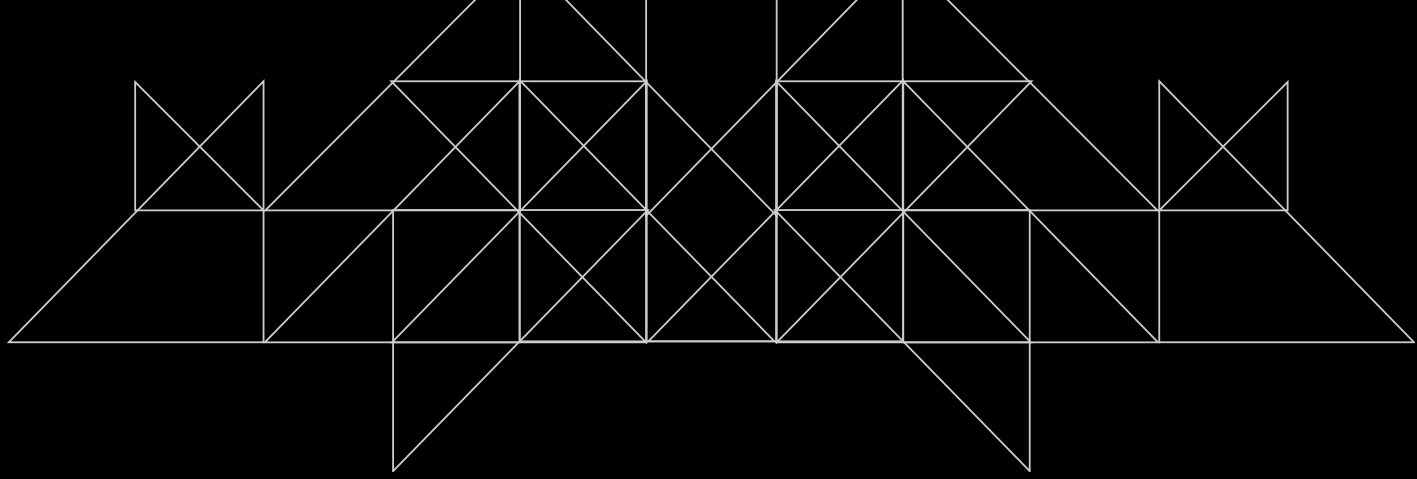
Our issues of each volume will be published online
IN
February, April, June, August, October, and December

reviewing process

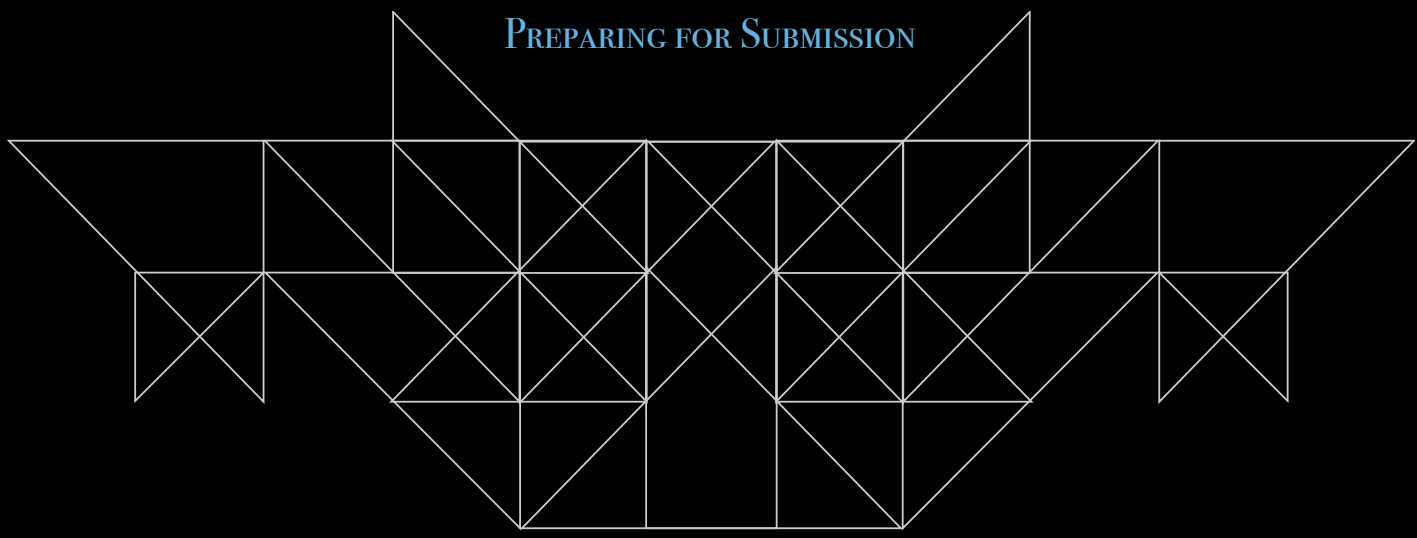
All accepted articles are classified into two main categories;
"***standard submission***" with the approximated processing time of 3-4 months and "***expression submission***" with the approximated processing time of 1-2 months. For the latter category, the author must submit as standard submission with notifying our journal for express submission.

Email: theclinicalacademia@gmail.com
Telephone: (+66) 088 328 1027

Contents



International Committee of Medical Journal Editors (ICMJE) Recommendation for Preparing for Submission



1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT for randomized trials, STROBE for observational studies, PRISMA for systematic reviews and meta-analyses, and STARD for studies of diagnostic accuracy. Journals are encouraged to ask authors to follow these guidelines because they help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, select¬ing, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network and the NLM's Research Reporting Guidelines and Initiatives.

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the Abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.
Author information: Each author's highest academic degrees should be listed, although some journals do not publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the Abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of Figures and Tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because Tables and Figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Conflict of Interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not over-interpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential. Funding sources should be listed separately after the Abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a

registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository, authors should state at the end of the abstract the data set name, repository name and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer)." Authors should define how they measured race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives–usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your finings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations Related to References

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests.Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications.

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Reference Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals: Sample References webpage and detailed in the

NLM's Citing Medicine, 2nd edition. These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For X-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

Time intervals and in-hospital delay in thrombolysis administration in acute ischemic stroke

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

Narudee Srisang, M.D.

Department of Emergency Medicine, Khon Kaen Hospital, Thailand

Accepted: January 2019
Latest revision: April 2019
Printed: April 2019

Correspondence to: Narudee Srisang; narudee_y@hotmail.com

ABSTRACT

OBJECTIVE
To determine the time intervals at the Emergency Department (ED) resulting in delayed thrombolytic therapy.

METHODS
This was a cross-sectional analytical study including 268 stroke fast track patients who admitted at ED of Khon Kaen Hospital, Thailand. Period of time for each patient was assessed before received thrombolytic drug. Door to needle (DTN) time more than 60 minutes was considered a delayed treatment. Time intervals that impact DTN time and accuracy of prediction were analyzed.

RESULTS
Of 88 with thrombolysis administration, there were 51 patients in the delayed group and 37 patients in the non-delayed group. The median DTN time was 75 minutes (interquartile range (IQR), 68 to 84) in the delayed group and 55 (IQR, 48 to 58) minutes in the non-delayed group. Final test to needle (FTN) time was the time interval that affected delayed treatment (adjusted odds ratio, 2.63; 95% confidence interval [CI], 1.33 to 5.13; P=0.005) and FTN time 34 minutes or longer had prognostic performance 90.4% (95% CI, 84.2 to 96.5), sensitivity 76.5% (95% CI, 62.5 to 87.2) and specificity 94.6% (95% CI, 81.8 to 99.3) to predict delayed thrombolysis administration.

CONCLUSION
In adults with acute ischemic stroke, FTN 34 minutes or longer was associated with the delay in thrombolysis administration.

INTRODUCTION

Stroke is the second cause of death in the population over the age of 60 years worldwide, people around the world die each year of stroke about 6 million people, and about 5 million people are permanent disabilities.[1] Its standard and the most acceptable treatment is thrombolytic therapy, starting drug early and within 4.5 hours since the onset of symptoms can improve outcome.[2-5] American Stroke Association has set the time frame of various processes as follows: the patients should receive a brain imaging within 25 minutes, interpreted by a specialist within 45 minutes and received thrombolytic drug within 60 minutes.[6] However, it is still found that most patients with acute ischemic stroke still do not receive the drug within the specified time.[7,8] There are studies regarding factor associated with an in-hospital delay in intravenous thrombolysis for acute ischemic stroke that focused on patient and hospital characteristics.[9-13] There is, however, limited study about time intervals before receiving the drug. Therefore, this study aimed to determine the time factors and treatment process for patients with acute ischemic stroke within the Emergency Department (ED) resulting in the delayed thrombolytic drug.

METHODS

PATIENTS AND OVERSIGHT

From January through December 2017, the cross-sectional analytical study was conducted at the ED, Khon Kaen Hospital, Thailand. All patients who presented with clinical signs of acute ischemic stroke which consists of slurred speech, arm weakness, face drooping, one or the other with symptoms, not more than 3 hours (stroke fast track, SFT) and 18 to 80 of age were eligible for the study. Criteria for exclusion were the duration of onset of symptom until receiving the thrombolytic drug was more than 270 minutes (4.5 hours) and incomplete time record data. The study was approved by the research ethics board of Khon Kaen Hospital, it was designed by the author and no industry support or funding. The results were collected and analyzed by the author, who vouch for the data.

IN-HOSPITAL STROKE FAST TRACK PROTOCOL

The processes when the stroke fast track patients arrived at the ED included an assessment by an emergency physician, informing the neurologist, sending the blood to test in laboratory examination, using brain imaging for the diagnosis of brain ischemia. The indications and contraindications were considered for giving thrombolytic drug and requesting consent from patients and relatives.

VARIABLES

The patient characteristics including age, sex, medical history i.e., diabetes mellitus, hypertension, dyslipidaemia, atrial fibrillation, prior stroke, current smoking and heavy drinking, baseline variables i.e., systolic blood pressure (SBP), diastolic blood pressure (DBP), blood sugar and National Institute of Health Stroke Scale (NIHSS); type of presenting including on their

Table 1. Characteristics of the patients

Characteristic	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)
Age, median (IQR), years	68 (61-75)	60 (56-73)
Male-no. (%)	32 (62.8)	19 (51.4)
Medical history-no. (%)		
Diabetes mellitus	16 (31.4)	14 (37.8)
Hypertension	26 (51.0)	21 (56.8)
Dyslipidemia	5 (9.8)	3 (8.1)
Atrial fibrillation	9 (17.6)	14 (37.8)
Hypertension	1 (2.0)	2 (5.4)
Current smoking	7 (13.8)	2 (5.4)
Heavy drinking	5 (9.8)	5 (13.5)
Baseline variables, median (IQR)-mmHg		
Systolic blood pressure	159 (139-173)	154 (136-170)
Diastolic blood pressure	88 (78-98)	91 (76-103)
Blood sugar	132 (104-162)	130 (107-161)
National Institute of Health Stroke Scale	10 (7-14)	12 (8-16)
Type of presenting -no. (%)		
On their own	6 (11.8)	4 (10.8)
Emergency Medical Service	8 (15.7)	7 (18.9)
Referred from other hospitals	37 (72.5)	26 (70.3)
Working day -no. (%)	33 (62.8)	24 (64.9)
Time of presenting -no. (%)		
8.00-16.00	29 (56.9)	27 (73.0)
16.00-24.00	18 (35.3)	10 (27.0)
00.00-8.00	4 (7.8)	0 (0.0)

Table 2. Treatment outcomes

Outcome	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)
Intracerebral hemorrhage-no. (%)	4 (7.8)	9 (24.3)
Brain herniation -no. (%)	11 (21.6)	8 (21.6)
Craniectomy -no. (%)	4 (7.8)	2 (5.4)
Death -no. (%)	6 (11.8)	5 (13.5)

own, Emergency Medical Service (EMS), refer; day and time of presenting; outcome including intracerebral hemorrhage, brain herniation, undergo craniectomy and dead were analyzed.

The time from symptom onset to administration of the thrombolytic drug was divided into the following intervals: the duration from the symptom onset to ED (onset to door, OTD), the duration from arrival at ED to evaluation by doctor (door to evaluation, DTE), the period from the arrival at ED until the blood was sent for laboratory examination (door to laboratory, DTL), the period from the arrival at the ED until receiving computerized brain tomography (door to imaging, DTI), the final examination completed (laboratory blood test or brain imaging results) until receiving thrombolytic drug (final test to needle, FTN), the duration of the occurrence of symptom until receiving thrombolytic drug (onset to needle, OTN) and the time since arriving at the ED until receiving a thrombolytic drug (door to needle, DTN).

STATISTICAL ANALYSIS

All calculations were performed using STATA 11.0 software. All analyses were based on comparison

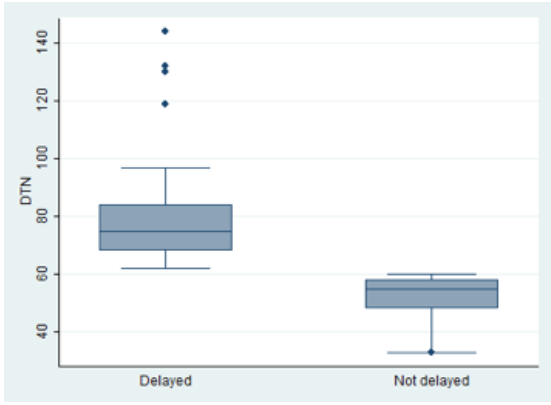


Figure 1. Door to needle times compare between delayed and not delayed group.

between the delayed DTN (>60 minutes) and non-delayed DTN. Quantitative variables were presented as median and interquartile ranges (IQR). Mann-Whitney U test was used to compare median between two groups. Binary logistic regression was used to identify the variables impacting DTN time. The factors that showed significant results in univariate analysis were included in the multivariate analysis, P≤0.05 was considered statistically significant to estimate the crude odds ratios (COR), adjusted odds ratios (AOR) and 95% confidence interval (CI). The accuracy, sensitivity, specificity with 95%CI were also analyzed using the receiver operating characteristic (ROC) curve to find the best cut-off points of the time interval.

RESULTS

There were 1,129 patients with acute ischemic stroke, 268 patients were in stroke fast track patients and 88 patients received thrombolytic drugs within 270 minutes; 51 in the delayed group

Table 3. Times intervals

Time interval-min	Delayed door to needle time (n=51)	Non-delayed door to needle time (n=37)	P Value
	Median (IQR)		
Onset to door	120 (85-155)	157 (120-189)	0.002
Door to evaluation	2 (0-7)	2 (0-5)	0.734
Door to laboratory	9 (5-14)	9 (7-11)	0.855
Door to imaging	24 (18-29)	20 (17-22)	0.024
Final test to needle	37 (34-46)	22 (15-25)	<0.001
Door to needle	75 (68-84)	55 (48-58)	<0.001
Onset to needle	202 (165-225)	213 (175-242)	0.323

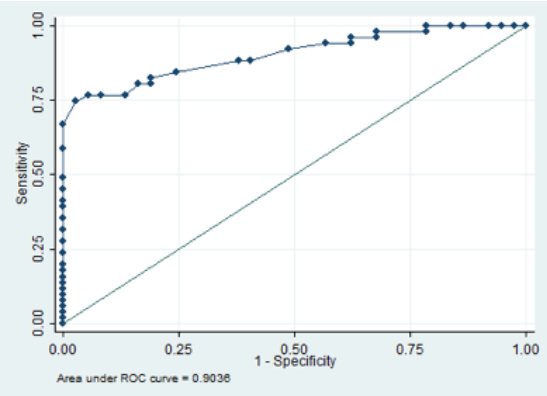


Figure 2. Receiver operating characteristic (ROC) curve for final test to needle (FTN) time ability to predict the delay in thrombolysis administration

and 37 in the non-delayed group. The characteristics of these 88 patients are shown in Table 1. Most of them were male with a median age of more than sixty years old. Generally, their characteristics were similar.

The number of patients with intracerebral hemorrhage after thrombolysis administration were more in the non-delayed group (Table 2). There were a similar numbers of death in both groups, all of them died from severe sepsis.

From the analyzing of various time factors comparing between the delayed and non-delayed group, it was found that the former tended to have shorter OTD (P=0.002) but longer DTI (P=0.024), longer FTN (P<0.001), and longer DTN (P<0.001) (Table 3).

From Table 4, it was found that longer OTD, DTI, and FTN were associated with the delay in thrombolysis administration (COR, 0.88; 95% CI, 0.77 to1.00, P=0.043; COR, 1.07; 95% CI, 1.01 to1.13, P=0.023; and COR, 1.22; 95% CI, 1.12 to1.33, P<0.001, respectively) from the univariable analysis. However, when the three periods were included in the binary logistic regression, it was found that only FTN was significantly associated with the delay in thrombolysis administration

Table 4. The association between time intervals and the delay in thrombolysis administration.

Variables	Crude odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
Onset to door-min	0.88 (0.77-1.00)	0.98 (0.95-1.02)
Door to imaging-min	1.07 (1.01-1.13)	0.93 (0.69-1.25)
Final test to needle-min	1.22 (1.12-1.33)	2.63 (1.33-5.18)

(AOR, 2.63; 95% CI, 1.33 to 5.18, P=0.005) while OTD and DTI were not.

When bringing the FTN period to computing the ROC curve, it was found that the duration from 34 minutes or more had prognostic performance 90.4% (95% CI, 84.2 to 96.5), sensitivity 76.5% (95% CI, 62.5 to 87.2) and specificity 94.6% (95% CI, 81.8 to 99.3) to predict the delay in thrombolysis administration (Figure 2).

DISCUSSION

In acute ischemic stroke patients with indications for treatment and no contraindications for the thrombolytic drug, the faster treatment indicate the better response and the reduction of complications. The present study found that the median DTN period was longer in the delayed group, although OTD period was shorter in the delayed group. This might be less eagerness for those coming early in the present study.

In the present study, FTN was the only factor found to be associated with the delay in thrombolysis administration. This might be due to the fact that this period is the time of the decision to consider the treatment which consists of several sub-processes, such as neurologist consultation, giving information and requesting consent from patients and relatives before prescribing the treatment. These findings were similar to that of the previous cohort study from China in 2015 with 202 patients with acute ischemic stroke, from the linear regression it found that the time interval of FTN greater than or equal to 30 minutes was associated the delay in thrombolysis administration due to the decision process of patients and relatives being concerned about complications from treatment and high drug prices.[14]

However, one retrospective case review from the US in 2017 with 487 patients with acute ischemic stroke with the thrombolysis administration it found that the delay of thrombolysis administration was associated with the delayed imaging.[15] Moreover, it also found that DTI more than [25] minutes was found in about half of the patients.15 Nonetheless, no study has been made to describe the appropriate time of FTN for prompt thrombolysis administration.

The limitation of the present study included its retrospective in nature. Thus, potential several sub-processes causes of the delayed FTN were unable to unretrievable. Therefore, the further study should focus on the process in the FTN period such as a final test to doctor decision, final

test to the patients' and relatives' decision, final test to drug preparation. It will determine the specific time interval that causes the delay in thrombolysis administration. This study was done in the only one tertiary hospital with the availability of support systems of diagnosis and treatment. Degree of generalization is, hence, limited

In conclusion, the FTN period of less than 34 minutes was associated with prompt thrombolytic administration. Further research with a larger sample and prospective in nature to confirm our findings is needed. Detail of sub-process of FTN should be verified for a better understanding of our care delivery.

ACKNOWLEDGMENTS & DECLARATION

This study can be accomplished with information from the Computer Center of Khon Kaen Hospital. Thank you to all emergency physicians who provided the opportunity and time to conduct research. I would like to thank Ms. Sri La Wong, who helped to find information and deliver relevant documents, and research staff at Khon Kaen Hospital for making this research work as smooth as possible.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

REFERENCES

1. Campaign W. Facts and Figures - World Stroke Campaign [Internet]. Worldstrokecampaign.org.2017 [cited 7 November 2017]. Available from:http://www.worldstrokecampaign.org/learn/factsand-figures.html
2. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–1587.
3. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. Neurology. 2000;55:1649–1655.
4. Clark WM, Albers GW, Madden KP, Hamilton S;Thrombolytic Therapy in Acute Ischemic Stroke Study Investigators. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke. 2000;31:811–816.
5. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768–774.
6. Jauch E, Saver J, Adams H, Bruno A, Connors J, Demaerschalk B et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare ProfessionalsFrom the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.
7. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, et al.; SITS investigators. Implementation and outcome of thrombolysis with alteplase 3–4.5 h after an acute stroke: an updated analysis from SITS-ISTR. Lancet Neurol. 2010; 9:866–874.
8. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years.Stroke. 2011; 42:1952–1955.
9. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011 Feb 22;123(7):750-8.
10. Köhrmann M, Schellinger PD, Breuer L, Dohrn M, Kuramatsu JB, Blinzler C, Schwab S, Huttner HB. Avoiding in hospital delays and eliminating the three−hour effect in thrombolysis for stroke. International Journal of Stroke. 2011 Dec;6(6):493-7.

11. Mikulík R, Kadlecová P, Czlonkowska A, Kobayashi A, Brozman M, Švigelj V, Csiba L, Fekete K, Korv J, Demarin V, Vilionskis A. Factors influencing in-hospital delay in treatment with intravenous thrombolysis. Stroke. 2012 Jun;43(6):1578-83.

12. Van Schaik SM, Scott S, de Lau LM, Van den Berg-Vos RM, Kruyt ND. Short door-to-needle times in acute ischemic stroke and prospective identification of its delaying factors. Cerebrovascular diseases extra. 2015;5(2):75-83.

13. Mohedano AI, Pastor AG, Arratibel AG, García PS, Otero FD, Delgado FR, Rubio RD, González AM, Alen PV, Bullido YF, Osorio JV. Factors associated with in-hospital delays in treating acute stroke with intravenous thrombolysis in a tertiary centre. Neurología (English Edition). 2016 Sep 1;31(7):452-8.

14. Qiang H, Qing-feng M, Juan F, Wei-yang C, Jian-ping J, Hai-qing S, Hong C, JianWu. Factors Associated with In-Hospital Delay inIntravenousThrombolysis for Acute Ischemic Stroke: Lessons from China. PLoSONE. 2015;10(11):1-9.

15. Ashkan M, Jordan D, Navdeep SL, Hamidreza RO, Christopher D, Peyman S, Marilou C, Annemarie C, Deborah AS, David J, Elad IL, Robert NS. Delays in door-to-needle time for acute ischemic stroke in the emergency department: A comprehensive stroke center experience. Journal of the Neurological Sciences. 2017;376:102–105.

Placental sites and preeclampsia in singleton pregnancy: a retrospective cohort study

ORIGINAL ARTICLE

ORIGINAL ARTICLE BY

Atiwat Unpikool[1], M.D.; Chayamak Sareeborvornthanasak [2], M.D.; Sutida Sonbankoh[3], M.D.

[1]Roi Et Hospital, Thailand; [2]Khon Kaen Hospital, Thailand; [3]Khon Kaen Hospital, Thailand.

Accepted: April 2019
Latest revision: April 2019
Printed: April 2019

Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To ascertain the association between placental sites and the development of preeclampsia.

METHODS

We conducted a retrospective cohort study of 1,080 singleton pregnant women with spontaneous delivery from May 2014 to January 2016 at Khon Kaen Hospital, Thailand comparing the development of preeclampsia between the lateral placental site and central placental site. The primary outcome was developing preeclampsia. The secondary outcomes were placental abruption, postpartum hemorrhage, preterm labor, intrauterine fetal death, low birth weight, macrosomia, APGAR score, birth weight, and placental weight.

RESULTS

A total of 1,080 records of singleton pregnant women were reviewed (257 in the lateral placental site group and 823 in the central placental site group). There was no significant difference between the two groups in the rate of developing preeclampsia; 24 pregnant women (9.3%) in former group and 60 pregnant women (7.3%) in later group (adjusted odds ratio [AOR], 0.67 95% confidence interval [CI], 0.39 to 1.16; P=0.151). Furthermore, there was no difference regarding placental abruption, postpartum hemorrhage, preterm labor, intrauterine fetal death, low birth weight, macrosomia, APGAR score, birth weight, and placental weight.

CONCLUSION

In singleton pregnant women with spontaneous delivery, we found no association between placental sites and developing preeclampsia.

INTRODUCTION

Preeclampsia was found approximately 5% of pregnancies worldwide in 2013 and was the result of nearly 10% of maternal death in Asia in 2006.[1-2] The abnormalities in the placental vasculature development can result in placental underperfusion and may lead to release of circulating antiangiogenic and other substances that can cause maternal systemic endothelial dysfunction, resulting in hypertension, proteinuria, and the other clinical manifestations.[3-7] The lateral placental site of the placenta may be a risk factor of abnormal placental blood flow leading to the development of preeclampsia.[7-10] Thus, the uterine artery Doppler is used as a reliable predictor for preeclampsia.[11-14]

There are many studies demonstrate the association between placental sites and preeclampsia but they are still controversy, for instance, the Indian study in 2012 with 150 pregnant women stated that females with lateral placental site were associated with five-time higher rate of preeclampsia,[15] another study from Turkey in 2015 with 1,057 patients also supported the findings that preeclampsia was significantly greater in lateral placental site group.[16] However, a prior study from Toronto, Canada in 2011 explained that the placental sites did not correlate with the rate of preeclampsia in 796 pregnant women.[17] Seeing that the association between placental implantation and preeclampsia is unclear. Hence, we conducted a retrospective cohort study to ascertain the association between placental sites and the development of preeclampsia.

METHODS

STUDY DESIGN

This retrospective cohort study to ascertain the association between insertion sites of the placenta and the development of preeclampsia was conducted at Khon Kaen Hospital, Thailand.

INCLUSION CRITERIA

We reviewed medical records of singleton pregnant women with spontaneous delivery at the hospital from May 2014 to January 2016.

EXCLUSION CRITERIA

All medical records of singleton pregnant women with spontaneous delivery indicated using the International Classification of Disease (ICD) 10. We recorded the characteristics consist of maternal age, gestational age, body mass index (BMI) at the first prenatal visit, total weight gain, gravidity, parity, previous abortion, previous preterm delivery, number of antenatal care, gestational diabetes, chronic hypertension, mild anemia, male infant and congenital anomalies.

EXPOSURE

Placental sites were classified as a lateral or central placental site using the record of the transabdominal ultrasonography performed by obstetrics and gynecology resident prior to delivery.

OUTCOMES

The primary maternal outcome was preeclampsia. The secondary maternal outcomes were placental abruption and postpartum hemorrhage. The

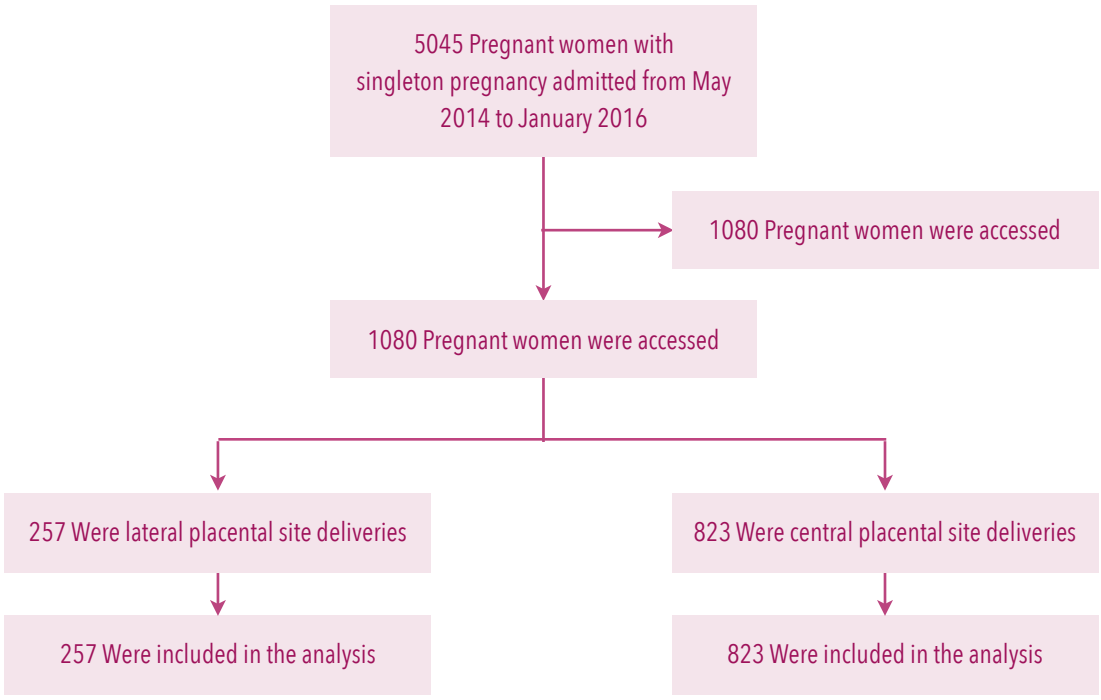


Figure 1. Represents inclusion and exclusion journal in this systematic review

secondary neonatal outcomes were preterm labor, intrauterine fetal death, low birth weight, macrosomia, APGAR score, birth weight, and placental weight.

STATISTICAL ANALYSIS

We used descriptive statistics to summarize characteristics of pregnancy in each group. We used number and percent for a categorical variable, mean and standard deviation (SD) for normally distributed continuous variables, the median and interquartile range for non-normally distributed continuous variables. For inferential statistics, categorical variables are compared using a chi-square test. We used student t-test for comparing normally distributed continuous variables and used the Mann-Whitney test for comparing non-normally distributed continuous variables. Event rate of primary and secondary outcomes between the two groups was analyzed regarding relative risk. Later, the adjusted odds ratio from logistic regression analysis and used to identify the relationship between exposure and outcomes of the study.

RESULTS

CHARACTERISTICS OF THE PREGNANT WOMAN

From May 2014 to January 2016, the medical records of 5,045 singleton pregnant women with spontaneous delivery at Khon Kaen Hospital were

reviewed. 3,965 of them were excluded because the data of placental sites were not available. Thus, 1,080 medical records of women were included in the analysis (Figure 1.).

For maternal characteristics, most of the women were in the first (45.4%) or second pregnancies (32.6%). Most of them had no history of abortion (81.8%) and no history of preterm (97.2%). Approximately 85% of them had more than 4 times for antenatal care. A relatively low proportion of them had gestational diabetes mellitus (5.6%), chronic hypertension (2.3%) and mild anemia (22.0%). The median age of singleton pregnant women was 24.9 years (IQR, 20.1 to 30.3) and their median gestational age at the time of delivery was 266.0 days (IQR, 252.0 to 278.8). Their median BMI at the first prenatal visit was 20.9 kg/m2 (IQR, 18.6 to 24.6). The median total weight gain was 12.4 kg (IQR, 9.0 to 16.0). For neonatal characteristics, a bit more than half were male (52.6%) and few were congenital anomalies (0.9%).

The characteristics between the two groups with lateral placental site and central placental site were no significant difference regarding gravidity (P=0.943), parity (P>0.999), proportion with history of abortion (P=0.201), number of antenatal care (P=0.845), proportion of gestational diabetes (P=0.893), proportion of chronic hypertension (P=0.330), proportion of mild anemia (P=0.867), proportion of male infant (P=0.500), proportion of congenital anomalies (P=0.303), age (P=0.956), gestational age (P=0.347) and total weight gain (P=0.871). Nevertheless, the former group had higher BMI at the first prenatal visit (P=0.044) and lower history of previous preterm delivery (P=0.010) (Table 1.).

STUDY OUTCOMES

Preeclampsia was diagnosed in 84 pregnancy. Comparing between the group with the lateral placental site and those with the central placental site, there was no significant difference between the two groups in developing preeclampsia (9.3% vs 7.3%; RR 1.28, 95% CI, 0.81 to 2.01; P=0.285) (Table 2.). Moreover, there were not different regarding placental abruption, postpartum hemorrhage, preterm labor, intrauterine fetal death, low birth weight, macrosomia, APGAR score, birth weight, and placental weight.

FACTOR PREDICTING PREECLAMPSIA

From the logistic regression analysis, the lateral placental site did not associate with developing preeclampsia (AOR 0.67; 95% CI, 0.39 to 1.16; P=0.151). The factors significantly increased the rate of developing preeclampsia were BMI at the first prenatal visit (AOR 1.15; 95% CI, 1.10 to 1.21; P<0.001) and total body weight gain (AOR 1.08; 95% CI, 1.03 to 1.12; P<0.001). Other factors including gravidity, parity, previous abortion, previous preterm delivery, number of antenatal care, gestational diabetes, chronic hypertension, mild anemia, male infant, congenital anomalies, maternal age, and gestational age were not associated with developing preeclampsia (Table 3.).

DISCUSSION

PRINCIPAL FINDINGS

In the present study, we found the rate of developing preeclampsia was no significant difference in pregnant women with the lateral

Table 1. Characteristics of pregnant women

Characteristic	Lateral placental site N =257 (23.8%)	Central placental site N =823 (76.2%)	P value
Maternal			
Gravidity-no. (%)			0.943
1	115 (44.7)	375 (45.6)	
2	86 (33.5)	266 (32.3)	
≥3	56 (21.8)	182 (22.1)	
PARITY-no. (%)			>0.999
0	138 (53.7)	440 (53.5)	
1	82 (31.9)	264 (32.1)	
2	30 (11.7)	96 (11.7)	
≥3	7 (2.7)	23 (2.8)	
Previous abortion-no. (%)			0.201
0	207 (80.5)	676 (82.1)	
1	48 (18.7)	125 (15.2)	
2	2 (0.8)	20 (2.4)	
≥ 3	0	2 (0.2)	
Previous preterm delivery-no. (%)			0.010
0	243 (94.6)	807 (98.1)	
1	12 (4.7)	14 (1.7)	
2	2 (0.8)	2 (0.2)	
Antenatal care 4 visits-no. (%)	38 (14.8)	128 (15.6)	0.766
Gestational diabetes-no. (%)	14 (5.7)	47 (5.9)	0.893
Chronic hypertension-no. (%)	8 (3.1)	17 (2.1)	0.330
Mild anemia-no. (%)	59 (23.9)	179 (23.4)	0.867
Maternal age-yr			0.956
Median	24.9	24.8	
Interquartile range	20.0-30.6	20.3-30.3	

Table 1. Characteristics of pregnant women			
Gestational age-day			0.347
Median	266.0	266.0	
Interquartile range	252.0-279.0	251.0-278.0	
BMI at the first prenatal visit-kg/m^2			0.044
Median	22.4	20.8	
Interquartile range	19.0-25.4	18.5-24.1	
Total weight gain -kg			0.871
Median	12.8	12.2	
Interquartile range	9.0-16.0	9.0-16.2	
Neonatal			
Male infant-no. (%)	140 (54.5)	428 (52.1)	0.500
Congenital anomalies -no. (%)	1 (0.4)	9 (1.1)	0.303

placental site as compared to those with the central placental site. There was also no significant difference in the rate of placental abruption, postpartum hemorrhage, preterm labor, intrauterine fetal death, low birth weight, macrosomia, and APGAR score below 7. The neonatal birth weight and placental weight were also similar between the two groups. However, high BMI at the first prenatal visit and high total body weight gain significantly increased the rate of developing preeclampsia.

STRENGTHS AND LIMITATIONS OF THE STUDY

This is the largest study to ascertain the association between placental sites and developing preeclampsia. The current study also has numerous strengths. We included medical records of all singleton pregnancy to reduce selection bias. All records were carefully reviewed and verified for missing data. We also double-entered data to reduce data collection error. From our findings, both groups of placental sites also had similar characteristics. However, our study has some limitations. absence of the data regarding placental sites was high. Recall bias is inevitable for instance data regarding weight before pregnancy. Our study was based on data from singleton pregnancy without thyrotoxicosis, previous cesarean section or uterine anomaly. Generalizability of our findings beyond these groups was then limited.

COMPARISON OF THE OTHER STUDIES

In our study, we found that the lateral placental site and the central placental site had no statistically significant difference in developing preeclampsia similar to the previous retrospective cohort study by

Table 2. The primary and the secondary outcomes

Outcomes	Lateral placental site N =257	Central placental site N =823	Relative risk (95% confidence interval)	P value
Maternal outcomes				
Preeclampsia-no. (%)	24 (9.3)	60 (7.3)	1.28 (0.81-2.01)	0.285
Placental abruption-no. (%)	0	4 (0.5)	0	0.578
Postpartum hemorrhage-no. (%)	3 (1.2)	11 (1.3)	0.87 (0.25-3.11)	0.834
Neonatal outcomes				
Preterm labor-no. (%)	92 (35.8)	310 (37.7)	0.95 (0.79-1.14)	0.588
Intrauterine fetal death-no. (%)	2 (0.8)	9 (1.1)	0.71 (0.15-3.27)	0.660
Low birth weight-no. (%)	64 (24.9)	238 (28.9)	0.86 (0.68-1.09)	0.211
Macrosomia-no. (%)	1 (0.4)	10 (1.2)	0.32 (0.04-2.49)	0.475
APGAR score-no. (%)				
At 1 min <7 points	15 (5.8)	50 (6.1)	0.96 (0.55-1.68)	0.888
At 5 min <7 points	2 (0.8)	12 (1.5)	0.53 (0.12-2.37)	0.538
At 10 min <7 points	2 (0.8)	8 (1.0)	0.80 (0.17-3.75)	>0.999
Birth weight-g				0.286
Median	2910.0	2850.0		
Interquartile range	2495.0-3240.0	2420.0-3230.0		
Placental weight-g				0.198
Median	700.0	640.0		
Interquartile range	600.0-700.0	600.0-700.0		

Devarajan et al., which showed no association between placental sites and perinatal outcomes in singleton pregnancy.[17] However, one retrospective cohort study, two prospective cohort study, and one case-control stated that preeclampsia was significantly greater in the lateral placental site. [8-9,15-16] Moreover, the current study mentioned that there was no significant difference in preterm labor between the lateral and the central placental site group. Although, Seckin et al study also described

Table 3. Factors predicting preeclampsia

Factors	Crude odds ratio (95% confidence interval)	P value	Adjusted odds ratio (95% confidence interval)	P value
Lateral site of placenta	0.76 (0.47-1.25)	0.286	0.67 (0.39-1.16)	0.151
Gravidity		0.468		0.879
1	1.00		1.00	
2	0.74 (0.43-1.28)		1.03 (0.29-3.69)	
>= 3	0.72 (0.40-1.29)		1.12 (0.43-3.51)	
Parity		0.251		0.496
0	1.00		1.00	
1	0.74 (0.22-2.54)		0.75 (0.12-4.69)	
2	0.61 (0.17-2.17)		0.43 (0.08-2.25)	
>= 3	1.22 (0.33-4.50)		0.74 (0.16-3.36)	
Number of antenatal care =< 4	0.82 (0.46-1.48)	0.511	0.66 (0.27-1.61)	0.758
Gestational diabetes	0.34 (0.17-0.68)	0.002	0.54 (0.24-1.19)	0.126
Chronic hypertension	0.20 (0.08-0.50)	0.001	0.44 (0.16-1.25)	0.125
Mild anemia	2.19 (1.11-4.33)	0.024	1.40 (0.68-2.88)	0.367
Male infant	1.35 (0.86-2.11)	0.194	1.38 (0.84-2.28)	0.203
Maternal age-yr	1.02 (0.99-1.06)	0.155	1.00 (0.95-1.04)	0.881
Gestational age-day	1.00 (0.99-1.01)	0.577	0.99 (0.98-1.00)	0.082
BMI at the first prenatal visit-kg/m^2	1.14 (1.09-1.19)	0.000	1.15 (1.10-1.21)	<0.001
Total weight gain-kg	1.04 (1.00-1.08)	0.025	1.08 (1.03-1.12)	<0.001

that preterm delivery was higher in the lateral placental site group.[16] This contradiction might be the different characteristics due to exclusion criteria of high-risk pregnancy and another one was the transabdominal ultrasonography in the second trimester and the sites can migrate until 32 weeks.

CONCLUSION AND IMPLICATION

The present study did not support the association between placental sites and developing preeclampsia in singleton pregnant women. Further prospective cohort study with a larger sample to confirm our findings is needed.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his supervision, guidance, and all of his support to help us complete the present study. We also would like to thank Khon Kaen Medical Education Center for all resources offered to us and Department of Medical Information System, Khon Kaen Hospital for data accessing.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

REFERENCES

1. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2013 Sep 1;170(1):1–7.
2. Khan, Khalid S et al. "WHO analysis of causes of maternal death: a systematic review." The lancet 367.9516 (2006): 1066-1074.
3. Contro E, Maroni E, Cera E, Youssef A, Bellussi F, Pilu G, et al. Unilaterally increased uterine artery resistance, placental location and pregnancy outcome. Eur J Obstet Gynecol Reprod Biol. 2010 Dec;153(2):143–7.
4. Fisher SJ. Why is placentation abnormal in preeclampsia? Am J Obstet Gynecol. 2015 Oct;213(4 Suppl):S115-122.
5. Maynard SE, Karumanchi SA. Angiogenic Factors and Preeclampsia. Semin Nephrol. 2011 Jan;31(1):33–46.
6. Zia S. Placental location and pregnancy outcome. J Turk Ger Gynecol Assoc. 2013 Dec 1;14(4):190–3.
7. Steegers EAP, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet. 2010 Aug 21;376(9741):631–44.
8. Yousuf S, Ahmad A, Qadir S, Gul S, Tali SH, Shaheen F, et al. Utility of Placental Laterality and Uterine Artery Doppler Abnormalities for Prediction of Preeclampsia. J Obstet Gynecol India. 2016 Feb 26;1–5.
9. Kofinas AD, Penry M, Greiss FC, Meis PJ, Nelson LH. The effect of placental location on uterine artery flow velocity waveforms. American Journal of Obstetrics and Gynecology. 1988 Dec;159(6):1504–8.
10. Ito, Yuji et al. "Resistance index of uterine artery and placental location in intrauterine growth retardation." Acta obstetricia et gynecologica Scandinavica 77.4 (1998): 385-390.
11. Meler E, Figueras F, Bennasar M, Gomez O, Crispi F, Gratacos E. The prognostic role of uterine artery Doppler investigation in patients with severe early-onset preeclampsia. Am J Obstet Gynecol. 2010 Jun;202(6):559.e1-4.
12. Rampello S, Frigerio L, Ricci E, Rota E, Lucianetti M, Parazzini F. Transabdominal uterine arteries Doppler at 12–14th and 20–24th week of gestation and pregnancy outcome: A prospective study. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2009 Dec;147(2): 135–8.
13. Oloyede OA, Iketubosin F. Uterine artery Doppler study in second trimester of pregnancy. Pan Afr Med J [Internet]. 2013 Jul 5 [cited 2016 Sep 5];15. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3810287/
14. Giordano R, Cacciatore A, Romano M, La Rosa B, Fonti I, Vigna R. Uterine artery Doppler flow studies in obstetric practice. J Prenat Med. 2010;4(4):59–62.
15. Kakkar T, Singh V, Razdan R, Digra SK, Gupta A, Kakkar M. Placental Laterality as a Predictor for Development of Preeclampsia. J Obstet Gynaecol India. 2013 Mar;63(1): 22–5.
16.Seckin KD, Cakmak B, Karsli MF, Yeral MI, Gultekin IB, Oz M, et al. Is lateral localisation of placenta a risk factor for adverse perinatal outcomes? J Obstet Gynaecol. 2015;35(7):696–8.
17. Devarajan K, Kives S, Ray JG. Placental location and newborn weight. J Obstet Gynaecol Can. 2012 Apr;34(4):325–9.
18. Ota, Erika et al. "Risk factors of pre-eclampsia/eclampsia and its adverse outcomes in low-and middle-income countries: a WHO secondary analysis." PloS one 9.3 (2014): e91198.
19. English, Fred A, Louise C Kenny, and Fergus P McCarthy. "Risk factors and effective management of preeclampsia." Integrated blood pressure control 8 (2015): 7.
20. Direkvand-Moghadam, Ashraf, Afra Khosravi, and Kourosh Sayehmiri. "Predictive factors for preeclampsia in pregnant women: a Receiver Operation Character approach." Arch Med Sci 9.4 (2013): 684-9.
21. Bartsch, Emily et al. "Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies." bmj 353 (2016): i1753.
22. Kiondo, Paul et al. "Risk factors for pre–eclampsia in Mulago Hospital, Kampala, Uganda." Tropical Medicine & International Health 17.4 (2012): 480-487.

23. Aksornphusitaphong, Adisorn, and Vorapong Phupong. "Risk factors of early and late onset pre–eclampsia." Journal of Obstetrics and Gynaecology Research 39.3 (2013): 627-631.
24. Levine, Richard J et al. "Circulating angiogenic factors and the risk of preeclampsia." New England Journal of Medicine 350.7 (2004): 672-683.
25. Agrawal, Sutapa, and Gagandeep K Walia. "Prevalence and risk factors for Pre-eclampsia in Indian women: a national cross sectional study." South Asia Network for Chronic Disease, Public Health Foundation of India, New Delhi (2010).
26. Kiondo, Paul et al. "Adverse neonatal outcomes in women with pre-eclampsia in Mulago Hospital, Kampala, Uganda: a cross-sectional study." The Pan African medical journal 17.Suppl 1 (2014).

Cryotherapy versus salicylic acid for treating plantar warts: a systematic review

SYSTEMATIC REVIEW

ORIGINAL ARTICLE BY

Farpratan Pongpanich[1], M.D.; Thitiphong Chaikasemsakun[2], M.D.; Natchaya Boonsarn[3], M.D.

[1]Thonburi Chumphon Hospital, Thailand; [2]Chum Phae Hospital, Thailand; [3]Srisaket Hospital, Thailand.

Accepted: April 2019
Latest revision: April 2019
Printed: April 2019

Correspondence to: Chutharat Thanchonnang; chuth.pp@gmail.com

ABSTRACT

OBJECTIVE

To identify the efficacy of cryotherapy and salicylic acid for treating plantar warts

METHODS

Three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus. We also sought for additional studies using a hand searching to explore other unidentified studies on the databases to identify all relevant randomized controlled trials comparing cryotherapy to topical salicylic acid in term of clearance of plantar warts.

RESULTS

We identified and included two randomized controlled trials with 309 participants with plantar warts. The clearance of plantar warts at 3 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 0.94; 95% CI 0.51 to 1.49, fixed-effect model, I^2=0) and at 6 months (RR 1.07; 95% CI, 0.79 to 1.46, fixed-effect model, I^2=0).

CONCLUSION

Clearance of plantar warts was not different between using cryotherapy and topical salicylic acid at 3 and 6 months.

INTRODUCTION

Plantar warts are caused by human papillomavirus especially type 1, 2, 27, and 57.[1-6] About 33% of primary schoolchildren have cutaneous warts and 20% have plantar warts.[7] Nearly 90% of them were located on pressure points such as the base of heels, longitudinal arch, metatarsal arch, or base of toes.[8] Patients with plantar warts seek for treatment for a variety of reasons, including discomfort, prevented from doing sports, interfering with work, bleeding and pain.[9-11,24] Treatments for plantar warts comprise salicylic acid, trichloroacetic acid, topical cidofovir, cryotherapy, hyperthermia therapy, laser, or debridement.[12-28]

There were two relevant studies; one of them mentioned that cryotherapy was statistically better than salicylic acid in the clearance of common warts.[25] However, both studies described no significant difference regarding the clearance of plantar warts between the two treatments.[24-25] We will conduct a systematic review in order to compare the clearance of plantar warts of the two treatments that might be clearer with larger sample size.

METHODS

SEARCH STRATEGIES

Without language restrictions, three independent reviewers systematically searched through electronic databases including Cochrane library, Pubmed, Trip Database and Scopus using the term "plantar warts" or "verruca plantaris" together with either "cryotherapy" or "salicylic acid". We applied MeSH searching to identify studies on Pubmed and Cochrane library. Furthermore, we sought for additional studies using a hand searching to explore other unidentified studies on the databases. All of the procedures above were described as individually searching by reviewers.

INCLUSION CRITERIA

STUDY DESIGN

Randomized controlled trial (RCT).

PARTICIPANTS

Plantar warts

INTERVENTIONS

Cryotherapy

COMPARISON

Topical salicylic acid

OUTCOMES

The clearance of plantar warts

EXCLUSION CRITERIA

We excluded records that were not be indicated as studies, then we removed the duplicated and ongoing studies. The rest of them were excluded using the following criteria (i) studies which plantar warts were not mentioned, (ii) studies which cryotherapy or salicylic acid were not indicated or were combined with other interventions known as treatments for plantar warts. The three reviewers individually identified and agreed to have two relevant studies after the inclusion and exclusion criteria to be included in the analysis

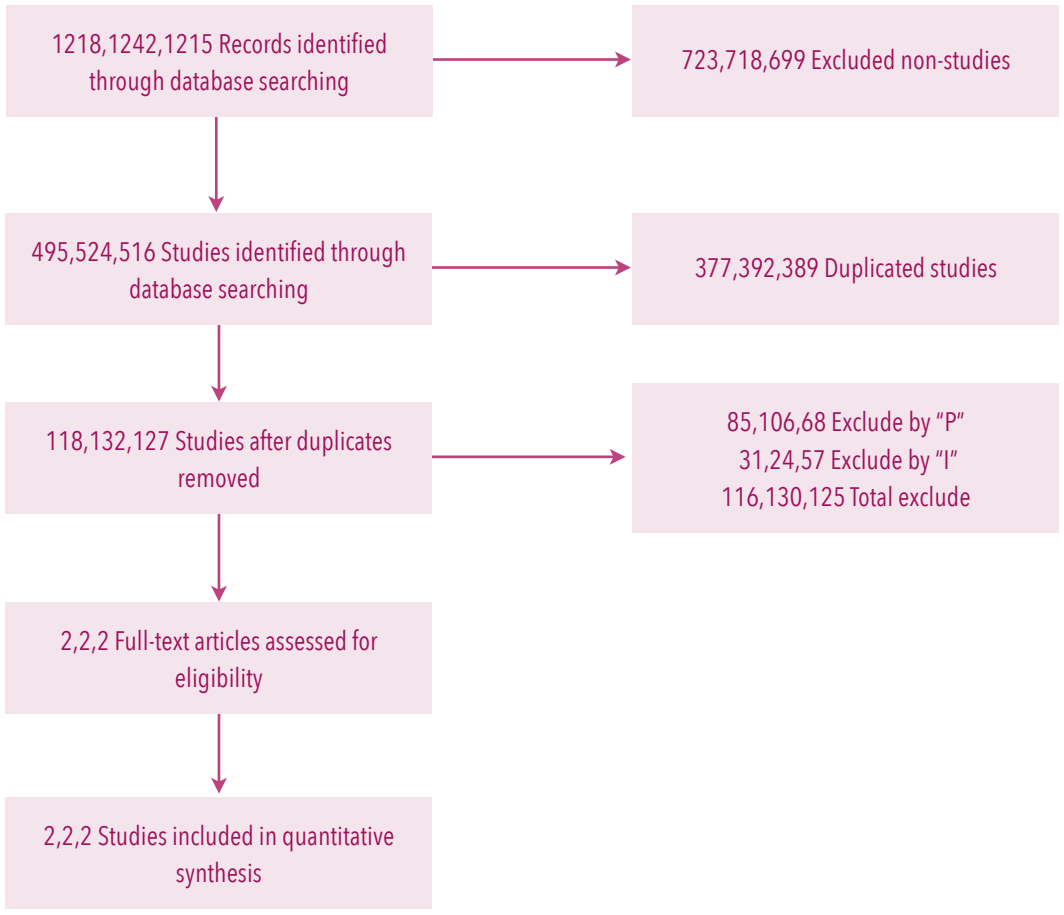


Figure 1. Represents inclusion and exclusion journal in this systematic review
Three numbers in each box are results from each process from each reviewer.

QUALITY OF REPORTING AND RISK OF BIAS

We used Jadad score to assess the quality of the included RCT comprising the evaluations of randomization, blinding methods and adequate description of withdrawals and drop-outs. In addition to this, we used Cochrane risk of bias to present the risk of bias demonstrated as random sequence generation, allocation concealment, blinding of participant and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias by classifying them to be three degrees which were low risk, high risk, and unclear risk of bias.

DATA EXTRACTION

We extracted the data from the included studies regarding the author, a number of patients, patient's age, duration of both treatments, duration of studies, interventions described as strength of salicylic acid as well as procedures of using

Table 1. Characteristics of 2 studies eligible for inclusion

Studies	Trial duration (months)	Number of patients with plantar warts	Age (Years)	Intervention	Clearance of plantar warts at 3 months Number of event/ Number in group (%)	Clearance of plantar warts at 6 months Number of event/ Number in group (%)
Cockayne et al	39	229	Median range 24.3 (12.2-75.3)	cryotherapy with liquid nitrogen by health care professional vs 50% Salicylic acid self-applied plantar warts every day.	Cryotherapy 15/110 (13.6%) Salicylic acid 17/119 (14.3)	Cryotherapy 33/98 (33.7%) Salicylic acid 29/95 (30.5%)
Bruggink et al	9	80	Range 4-79	cryotherapy with liquid nitrogen every 2 weeks by health care professional vs 40% Salicylic acid self-applied plantar warts every day.	Cryotherapy 11/37 (29.7.%) Salicylic acid 14/43 (32.6%)	Cryotherapy 18/37 (48.6%) Salicylic acid 20/42 (47.6%)

cryotherapy and outcomes in term of clearance of plantar warts from each study.

DATA ANALYSES

We calculated and described the results as the relative risk (RR) and 95% confidence interval (CI) by using Review Manager 5.3 statistical software to analyze the clearance of plantar warts between cryotherapy and salicylic acid at 3 and 6 months. We calculated I2 to show the heterogeneity among studies. Moreover, the results from a meta-analysis of our systematic review were described by forest plot. We used fixed-effect models for combining data in a meta-analysis. The publication bias was demonstrated in funnel plots.

RESULTS

STUDY CHARACTERISTICS

The searching results were totally identified as 1218, 1242 and 1215 records by the reviewers I, II and III, respectively (Figure 1). We identified 494, 523 and 515 records as studies, which 375, 390 and 387 of them were duplicates. There were 119, 133 and 128 studies remained after duplicate removed. We later excluded 117, 131, 126 studies because of being related to our exclusion criteria. The remaining two trials were included in the meta-analysis.[24-25] Both studies were compared topical salicylic acid to cryotherapy in term of clearance of plantar warts. The characteristics of 309 participants

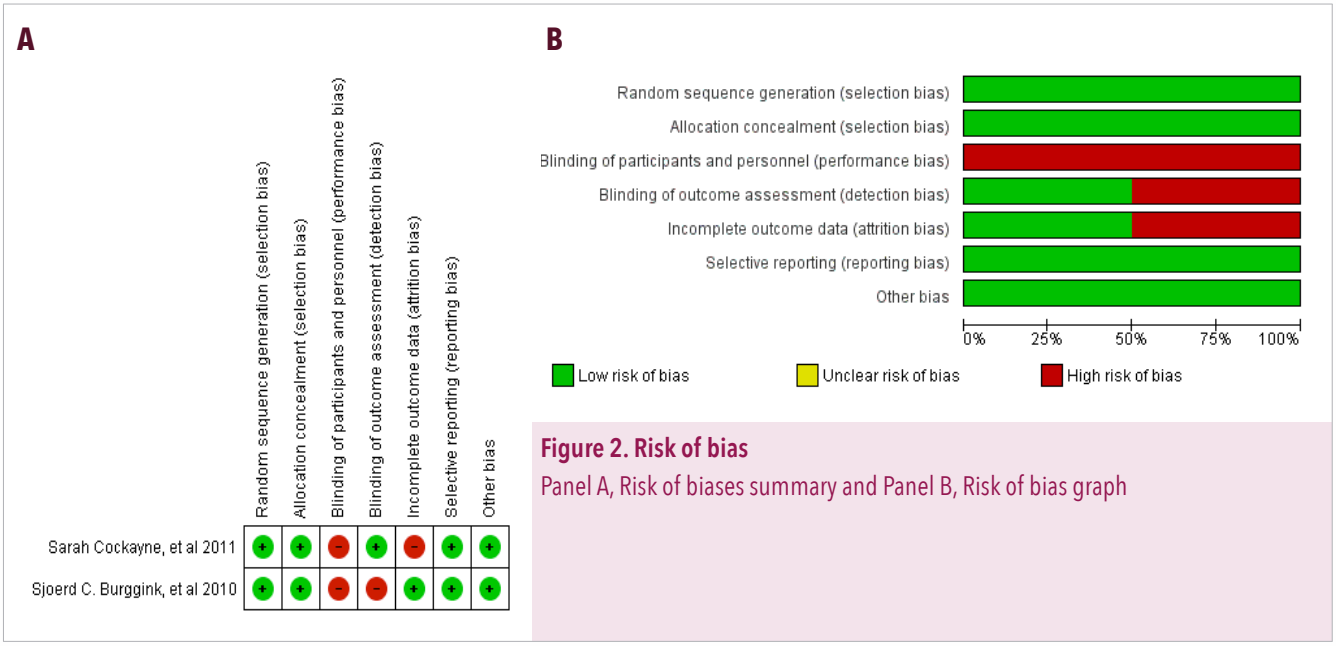


Figure 2. Risk of bias

Panel A, Risk of biases summary and Panel B, Risk of bias graph

with plantar warts in two RCTs are presented in Table 1.

ASSESSING THE QUALITY AND RISK OF BIAS

The quality of the two studies, Cockayne et al's study and Bruggink et al., 2010's study, was assessed using Jadad score and Cochrane Collaboration's tool was used to assess risks of bias. The former study had 2 points from the Jadad score (Table 3) because patients and physicians were not blinded and the dropouts were not described clearly at the end of the study. The later study had 3 points from the Jadad score because the study lacked only double-blinded method. The risk of bias using the tool of both studies is summarised in Figure 2.

RANDOM SEQUENCE GENERATION

Both studies reported the methods of random sequence.

ALLOCATION CONCEALMENT

The former study reported treatment allocation processed by telephoning or accessing a secure web randomization program, whereas, the latter study used opaque, sealed envelopes that were number based on computerization list delivered by an independent statistician.

BLINDING OF PARTICIPANT AND PERSONAL

Both studies were described as high risk of bias because the former study was an open trial and the later study mentioned those uncured patients in the 13th week could switch to other treatments by their own.

BLINDING OF OUTCOME ASSESSMENT

The former study evaluated the clearance of plantar warts using blinded digital photograph assessors which were considered as a low risk of bias. Evaluation of clearance of plantar warts of the later

Table 2. Meta-analysis of clearance of plantar warts comparing cryotherapy to salicylic acid at 3 and 6 months.

	Number of event/Number in group (%)		Relative risk	95% confidence interval	P Value
	Cryotherapy	Salicylic acid			
Clearance of plantar warts at 3 months	26/147(17.7)	31/162(19.1)	0.94	0.59-1.49	0.78
Clearance of plantar warts at 6 months	51/135(37.8)	49/137(35.8)	1.07	0.78-1.45	0.68

Table 3. Jadad score

	Cockayne et al	Bruggink et al
Was the study described as randomized ?	1	1
Was the method used to generate the sequence of randomization described and was it appropriate?	1	1
Was the study described as double blind ?	0	0
Was the method of double blind described and was it appropriate ?	0	0
Was there a description of withdrawals and dropouts ?	0	1
Score	2	3

study was considered as a high risk of bias because they could know the intervention.

INCOMPLETE OUTCOME DATA

The former study was a high risk of bias because they describe nothing about missing patients at 6-month evaluation. The later study described clearly of all missing data which were low risk of bias.

SELECTIVE REPORTING

Both studies were low risks of bias because all results were totally reported.

OTHER POTENTIAL SOURCES OF BIAS

No other sources of bias were mentioned in both studies. We described them as low risk of bias.

THE PRIMARY OUTCOME

THE CLEARANCE AT 3 MONTHS

Comparing cryotherapy to topical salicylic acid, the clearance of plantar warts at 3 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 0.94; 95% CI 0.51 to 1.49, fixed-effect model, $I^2=0$) (Figure 3).

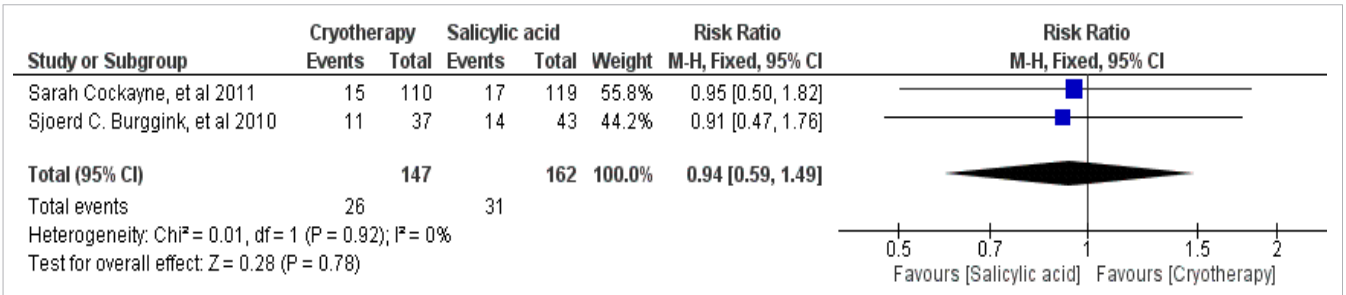


Figure 3. Forest plot: cryotherapy versus salicylic acid, outcome: 1.1 Clearance of plantar warts at 3 months

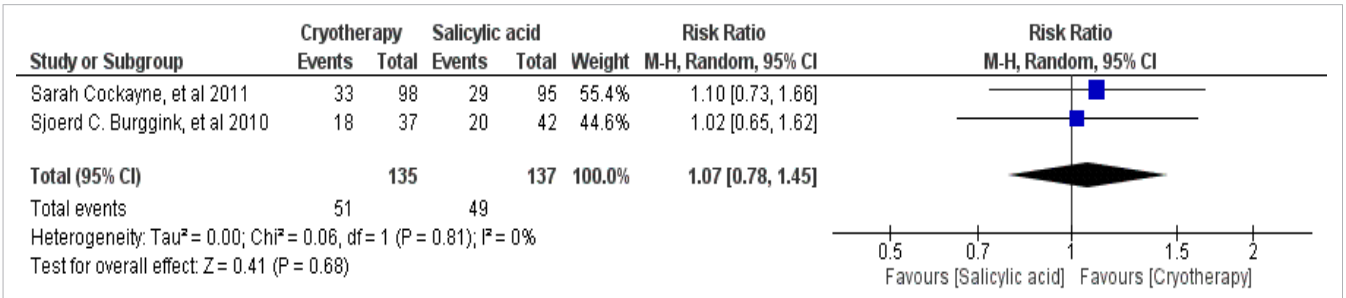


Figure 4. Forest plot: cryotherapy versus salicylic acid, outcome: 1.2 Clearance of plantar warts at 6 months

THE SECONDARY OUTCOME

THE CLEARANCE AT 6 MONTHS

Comparing cryotherapy to topical salicylic acid, the clearance of plantar warts at 6 months was interpreted that using cryotherapy was no statistically significant difference from using topical salicylic acid (RR 1.07; 95% CI, 0.79 to 1.46, fixed-effect model, I^2=0) (Figure 4).

ADVERSE EFFECT

Bruggink et al., 2010 reported that 62 participants had adverse effects. The pain was reported 84% as the most common side effect of cryotherapy while skin irritation was reported 53% as the most common side effect of salicylic acid. The other side effects were described in the table below.

PUBLICATION BIAS

The funnel plots of clearance of plantar warts at 3 and 6 months were not adequately interpreted the publication bias because our systematic review had only two RTCs that we could not detect the distribution of the studies properly (Figure 5-6).

DISCUSSION

SUMMARY OF EVIDENCE

In our systematic review, two RCTs were identified with 309 patients with plantar warts were included in the analysis and we found no statistically significant difference in clearance of plantar warts between cryotherapy and topical salicylic acid at 3 and 6 months. High homogeneity was observed. Both studies were conducted in patients aged 4

Table 4. Adverse effects reported at 13th week in Bruggink et al., 2010's study.

Type of side effect	Cryotherapy (n=37) Number of patients	Salicylic acid (n=40) Number of patients
Pain	31	4
Blistering	16	5
Scarring	1	-
Skin irritation	6	21
Skin pigmentation	3	2
Bleeding after filing	-	1
Crust	1	-
Other minor side effect	4	4

years or older. Meta-analysis of the adverse effects were not performed as only one study reported the effects by Bruggink et al., 2010, another study did not describe adverse effects clearly but only non-serious effects were mentioned by Cockayne et al. In our review, the funnel plots of the outcomes were summarised However, we did not estimate publication bias as the number of the included studies was too few.

STRENGTH AND LIMITATIONS OF THE REVIEW

To our knowledge, this is the first systematic review comparing cryotherapy to topical salicylic acid in the clearance of plantar warts. We conducted this review with the compliance to the Cochrane handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist, our search was comprehensive, no study likely to be missed. Moreover, I^2 was calculated as 0%. Thus,

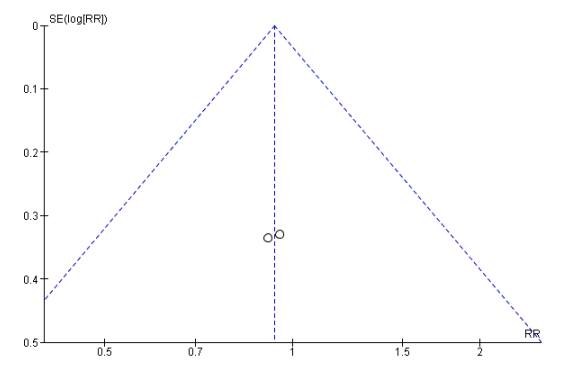


Figure 5. Funnel plot: cryotherapy versus salicylic acid, outcome: 1.1 Clearance of plantar warts in 3 months

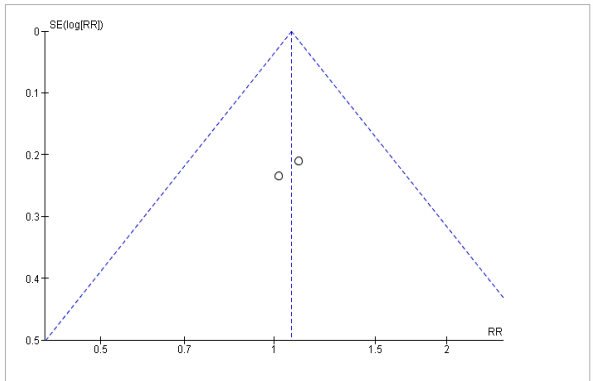


Figure 6. Funnel plot: cryotherapy versus salicylic acid, outcome: 1.2 Clearance of plantar warts in 6 months

our results are reproducible with high confidence for generalizability to other settings.

Our study had some limitations. The first limitation was the small number of participants because we found only two RCTs that followed our robust inclusion and exclusion criteria. The quality of the two RCTs was varied. Randomization and methods were adequately described in both trials. However, the study by Cockayne et al did not describe dropouts after 13th week clearly. Thus, the exact outcomes of both benefit and harm were not clearly identified due to the dropout. The third limitation was the blinding outcome bias as only the study by Cockayne et al, the assessors were blinded. The last limitation of our study was indicated as no description of double-blinded methods as both physicians and patients obviously knew one's intervention.

COMPARISON TO OTHER STUDIES

In our systematic review, there was no statistically significant difference in clearance of plantar warts between cryotherapy and salicylic acid at 3 and 6 months in patients aged 4 and over. Our findings were congruent to that of two prior studies that compared cryotherapy with salicylic acid plus lactic acid in patients with plantar warts and palmar warts.[23,26] Furthermore, Bruggink et al., 2015 described no difference between using cryotherapy and monochloroacetic acid in the clearance of common warts.[13] However, KaÇar et al's study described that salicylic acid plus cantharidin-podophyllotoxin was better than cryotherapy in the clearance of plantar warts.[28]

In our opinion, we could not suggest that chemical therapies were superior to physical therapies by evidence of referral studies mentioned above.[23,26,28] Although, one of them stated that combined chemical therapy was better than cryotherapy alone but no treatment would be indicated as the most effective one because the proper treatment needed to be considered carefully in every single case.

CONCLUSION AND IMPLICATION

There was no statistically significant difference between cryotherapy and topical salicylic acid in the clearance of plantar warts at three and six months. Despite no difference between cryotherapy and salicylic acid in term of clearance of plantar warts, we prefer salicylic acid to cryotherapy because of its affordability and availability, especially in developing countries. For the further upcoming studies, we suggest a large number of participants and a longer follow-up trial evaluate the differences in term of clearance of plantar warts as well as their recurrence between cryotherapy and topical salicylic acid.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to thank Dr. Thammasorn Jeeraaumponwat for his supervision, guidance, and all of his support to help us complete the present study. We also would like to thank Khon Kaen Medical Education Center for all resources offered to us and Department of Medical Information System, Khon Kaen Hospital for data accessing.

COMPETING INTERESTS: This study has no competing on interest.
FUNDING:None

REFERENCES

1. Orth G, Favre M, Croissant O. Characterization of a new type of human papillomavirus that causes skin warts. Journal of virology. 1977;24(1):108–120.
2. Bruggink SC, Gussekloo J, de Koning MNC, Feltkamp MCW, Bavinck JNB, Quint WGV,et al HPV type in plantar warts influences natural course and treatment response: secondary analysis of a randomised controlled trial. J Clin Virol. July 2013;57(3):227–32.
3. De Villiers E-M. Heterogeneity of the human papillomavirus group. Journal of virology. 1989;63(11):4898.
4. Rose RC, Bonnez W, Da Rin C, McCance DJ, Reichman RC. Serological differentiation of human papillomavirus types 11, 16 and 18 using recombinant virus-like particles. Journal of general virology. 1994;75(9): 2445–2449.
5. Whitaker JM, Palefsky JM, Da Costa M, King CM, Johnston JS, Barbosa P. Human papilloma virus type 69 identified in a clinically aggressive plantar verruca from an HIV-positive patient. J Am Podiatr Med Assoc. February 2009;99(1):8–12.
6. de Koning MNC, Quint KD, Bruggink SC, Gussekloo J, Bouwes Bavinck JN, Feltkamp MCW et al. High prevalence of cutaneous warts in elementary school children and the ubiquitous presence of wart-associated human papillomavirus on clinically normal skin. Br J Dermatol. January 2015;172(1): 196–201.
7. de Haen M, Spigt MG, van Uden CJ, van Neer P, Feron FJ, Knottnerus A. Efficacy of duct tape vs placebo in the treatment of verruca vulgaris (warts) in primary school children. Archives of pediatrics & adolescent medicine. 2006;160(11):1121–1125.
8. Williams HC, Pottier A, Strachan D. The descriptive epidemiology of warts in British schoolchildren. British Journal of Dermatology. 1993;128(5):504–511.
9. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australasian journal of dermatology. 2003;44(3):169–173.
10. Ciconte A, Campbell J, Tabrizi S, Garland S, Marks R. Warts are not merely blemishes on the skin: A study on the morbidity associated with having viral cutaneous warts. Australasian journal of dermatology. 2003;44(3):169–173.
11. Plantar Warts and Palmer Warts: Treatments and Causes [Internet]. [30 August 2016]. Available at:http://www.webmd.com/skin-problems-and-treatments/guide/plantar-warts-palmer-warts#1
12. El-Tonsy MH, Anbar TE-D, El-Domyati M, Barakat M. Density of viral particles in pre and post Nd: YAG laser hyperthermia therapy and cryotherapy in plantar warts. International journal of dermatology. 1999;38(5):393–398.
13. Bruggink SC, Gussekloo J, Egberts PF, Bavinck JNB, de Waal MWM, Assendelft WJJ et al. Monochloroacetic acid application is an effective alternative to cryotherapy for common and plantar warts in primary care: a randomized controlled trial. J Invest Dermatol. May 2015;135(5):1261–7.
14. Cengiz FP, Emiroglu N, Su O, Onsun N. Effectiveness and safety profile of 40% trichloroacetic acid and cryotherapy for plantar warts. J Dermatol. 4 April 2016;
15. Huo W, Gao X, Sun X, Qi R, Hong Y, Mchepange UO et al. Local Hyperthermia at 44°C for the Treatment of Plantar Warts: A Randomized, Patient–Blinded, Placebo–Controlled Trial. The Journal of Infectious Diseases. 15 April 2010;201(8):1169–72.
16. Prasad AJR. Targeted cryotherapy using disposable biopsy punches. Journal of cutaneous and aesthetic surgery. 2014;7(2): 118.
17. El-Mohamady AE-S, Mearag I, El-Khalawany M, Elshahed A, Shokeir H, Mahmoud A. Pulsed dye laser versus Nd: YAG laser in the treatment of plantar warts: a comparative study. Lasers in medical science. 2014;29(3):1111–1116.
18. Hashmi F, Torgerson D, Fairhurst C, Cockayne S, Bell K, Cullen M, et al. EVerT2–needling versus non-surgical debridement for the treatment of verrucae: study protocol for a single-centre randomised controlled trial. BMJ open. 2015;5(11):e009406.
19. Harika C, Sankeerth V, Jagannath Kumar V. Comparative efficacy of Electrosurgery with topical 50% Trichloroacetic acid in treatment of warts. [30 August 2016]; Available at http://jphmr.com/wp-content/uploads/2015/05/2.pdf
20. Kollipara R, Ekhlassi E, Downing C, Guidry J, Lee M, Tyring SK. Advancements in pharmacotherapy for noncancerous manifestations of HPV. Journal of clinical medicine. 2015;4(5):832–846.
21. Kauvar AN, McDaniel DH, Geronemus RG. Pulsed dye laser treatment of warts. Archives of Family Medicine. 1995;4:1035–1041.
22. Gibbs S, Harvey I. Topical treatments for cutaneous warts (Review). 2009 [30 August 2016]; Available at: http://xa.yimg.com/kq/groups/13708666/1582580719/name/verrugas.pdf
23. Steele K, Irwin WG. Liquid nitrogen and salicylic/lactic acid paint in the treatment of cutaneous warts in general practice. JR Coll Gen Pract. 1988;38(311):256–258.
24. Cockayne S, Hewitt C, Hicks K, Jayakody S, Kang'ombe AR, Stamuli E et al . Cryotherapy versus salicylic acid for the treatment of plantar warts (verrucae): a randomised controlled trial. BMJ. 2011;342:d3271.
25. Bruggink SC, Gussekloo J, Berger MY, Zaaijer K, Assendelft WJJ, de Waal MWM et al. Cryotherapy with liquid nitrogen versus topical salicylic acid application for cutaneous warts in primary care: randomized controlled trial. CMAJ. 19 OOctober 2010;182(15):1624–30
26. An assessment of methods of treating viral warts by comparative treatment trials based on a standard design - BUNNEY - 1976 - British Journal of Dermatology - Wiley Online Library [Inter]. [7 September 2016]. Available at http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2133.1976.tb05167.x/abstract

27. Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, et al. Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts: an economic decision model. 2006 [7 September 2016]; Available at http://eprints.nottingham.ac.uk/869/1/Thomas_HTA_warts_monograph2006.pdf
28. Kaçar N, Taşlı L, Korkmaz S, Ergin S, Erdoğan BŞ. Cantharidin-podophylotoxin-salicylic acid versus cryotherapy in the treatment of plantar warts: a randomized prospective study. J Eur Acad Dermatol Venereol. July 2012;26(7):889–93.

Atypical chromoblastomycosis presented as generalized eczema-like lesions

CASE REPORT

ORIGINAL ARTICLE BY

Vich Thampanya[1], M.D.; Rataporn Ungpakorn [2], M.D.;

[1]Chiangrai General Hospital, Thailand, [2]Faculty of Medicine, Chulalongkorn University, Thailand,

Accepted: February 2019
Latest revision: April 2019
Printed: April 2019

Correspondence to: Vich Thampanya; VICH.TA@cpird.in.th

PRESENTATION OF THE CASE

A 65-year-old gardener came to the hospital with pruritic, erythematous indurated plaques and patches on his face, trunk, and scrotum for 1 year. He was treated with topical corticosteroid for eczema before the consultation. A skin examination showed ill-defined erythematous pruritic patches and plaques with scattered scales and small areas of brownish-black dots on the chest and both axilla. Similar lesions were seen on the scrotum, but no brownish dots were noted (Figures 1). Other symptoms were unremarkable.

Table 1: Direct examination under 40x microscopy: Brownish, coin-like yeasts (sclerotic bodies).

Differential diagnosis		
Disease	**Accessible issues**	**Inaccessible issues**
Atypical chromoblastomycosis presented with generalized eczema-like lesions	Lesions with black dots Staining from lesions found sclerotic bodies Non-responsive lesions to steroids Culture for fungi found Cladosporium spp.	Due to the number of lesions are greater than in classical cases.
Eczema	Itching at the lesional areas The distribution of the rash could be generalized	Non-responsive lesions to steroids. Despite the positions of lesions should respond well to it.
Scabies	The position of the disease is compatible with scabies.	Lesions with black dots Staining from lesions found sclerotic bodies
Dermatophytosis	Itching which is found in patients with dermatophyte infection.	Characteristics of lesions without circular characteristics Lesions with black dots Staining from lesions found sclerotic bodies

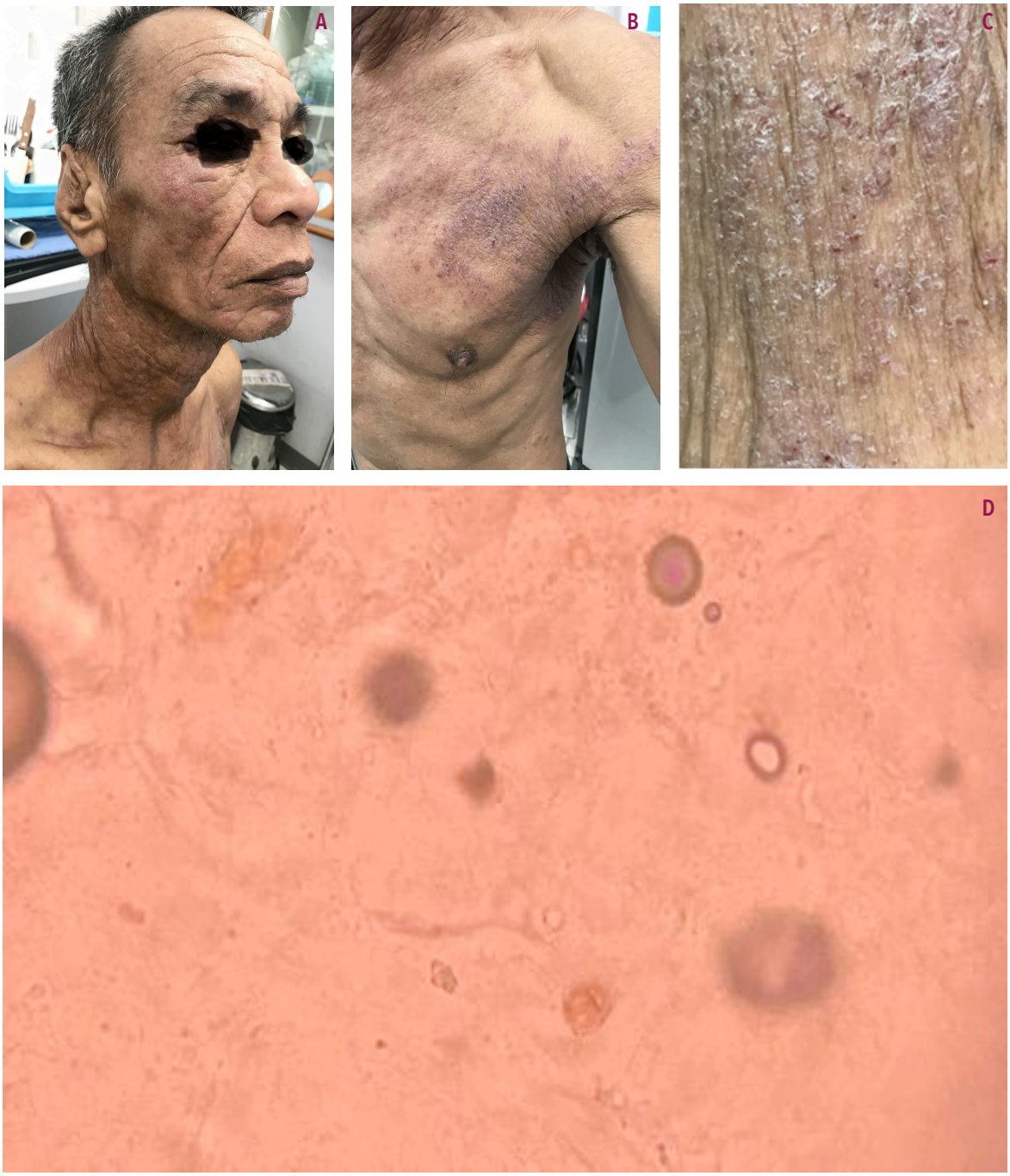
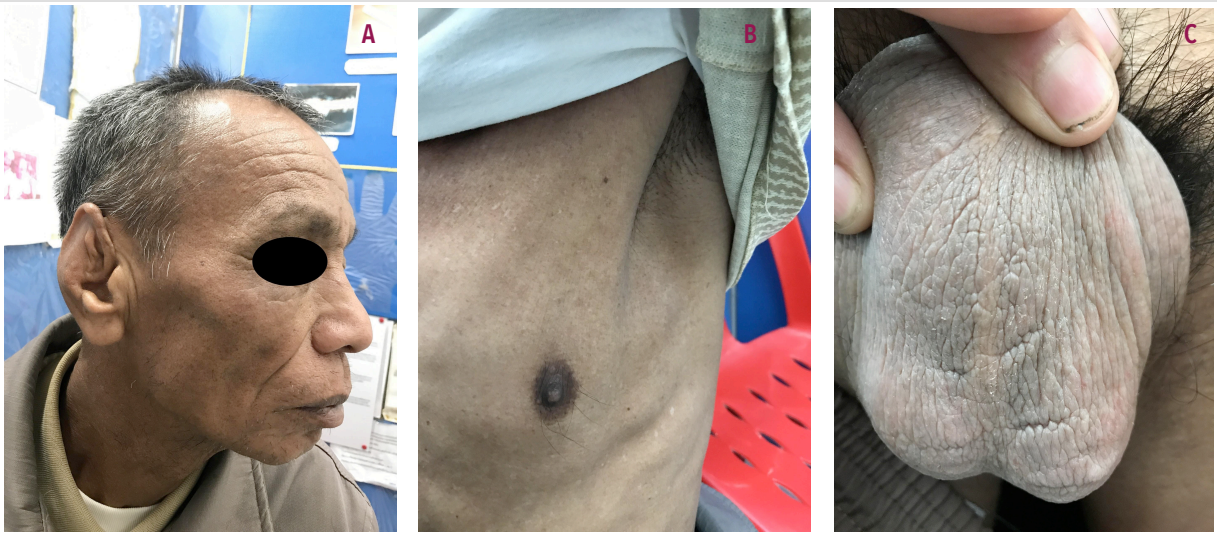


Figure 1.Eczematous-like eruptions
Panel A, a lesion on the face; Panel B, a lesion on the chest; Panel C, a scrotal lesion; Panel D, brownish dots from direct examination under a microscope from the scaly area on the chest



Figures 2: Improvement of all lesions after 5 months treatment with oral itraconazole 100 mg daily
Panel A, the subsided lesions on the face; Panel B, the subsided lesion on the chest; Panel C, the subsided scrotal lesion.

Direct skin examination under a microscope showed brownish, coin-shaped, sclerotic bodies. *Cladosporium spp*. was identified from a specimen culture. The blood biochemistry results were unremarkable.

CLINICAL DIAGNOSIS

Eczema with id eruption as the first visit. Laboratory data above aiding in forming the definite diagnosis as atypical chromoblastomycosis (CMB) presented as generalized eczema-like lesions later due to atypical presentations.

TREATMENT & DISCUSSION

The diagnosis of CMB was made based on the clinical presentation and mycologic confirmation. An oral itraconazole 100 mg once the daily dosage was initiated. Skin lesions improved after 4 weeks and cleared after 5 months (Figures 2). Mild itching persisted at the scrotal area but a KOH scraping was negative for evidence of fungus. CMB is a chronic fungal infection of the skin and subcutaneous tissue caused by a skin-to-skin fungal infection of a specific fungal group that occurs in tropical and subtropical areas around the world.[1]

Most cases affect the legs, especially the feet that are exposed to infected material. Palms, arms and buttocks are frequently infected while ear, cornea, neck, face, breast, chest and stomach are sporadically reported in the literature.

The disease can be presented clinically in 5 different forms: nodular, tumoral, verrucous, plaque and cicatricial. Our patient may be classified as plaque type. Normally, the pathogen for CMB is usually caused by *Fonsecaea pedrosoi*, *Phialophora verrucosa, Cladophialophora carrionii.* [2] Punkae Mahaisavariya et al, presented that CMB was caused by *C. carrionii and F. compactum* and responded well with itraconazole orally.[3]

The choice of treatment methods and the success of treatment depends on the etiological organism, size, extent, and location of the lesion. Bonifaz et al. analyzed 52 cases showing that itraconazole therapy can be applied for extensive lesions.[2] Mild and moderate forms may be successfully cured after 6–12 months. After the termination of therapy relapses are frequent, presumably because itraconazole is fungistatic. In the case of generalized CMB, as with this patient, the treatment is expected to be prolonged and have possible recurrences.[2,4]

There has been no report of patients with widespread eczematous-like rashes with neither the specific disease nor systemic symptoms as in this patient [5,6]. The diagnosis requires experienced clinical observation. The patient's profession may have relevance to the source of the infection.

CONCLUSION OF THE CASE

This is a rare atypical case report of CMB presented as generalized eczema-liked lesions without systemic symptoms. The detection of sclerotic bodies on the lesions helped lead to the diagnosis. Treatment with oral itraconazole was effective. Neither complications nor recurrences were found.

REFERENCES

1. Queiroz-Telles F. Chromoblastomycosis: a neglected tropical disease. Rev Inst Med Trop Sao Paulo.2015;57 Suppl 19:46-50

2. Paweł M. Krzyściak, Małgorzata Pindycka-Piaszczyńska, and Michał Piaszczyński. Chromoblastomycosis. Postepy Dermatol Aleregol. 2014

3. Mahaisavariya P, Chiprasert A, Sirayathom A, Khemngern S. Deep fungal and higher bacterial skin infections in Thailand: clinical manifestations and treatment regimens. Int J dermatol. 1999;38:279-84

4. Ungpakorn R. Mycoses in Thailand: current concerns. Nihon Ishinkin Zasshi. 2005; 46:81-6

5. Sugawara M, Sobajimay Y, Tamura H.A Case of Generalized Chromoblastomycosis.Acta Pathol Jpn. [Internet] [cited 2018 April 15]. Available from https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1440-1827.1964.tb01184.x

6. Radouane N, Hali F, Khadir K, Soussi M, Ouakadi A. Marouane S, Zamiati S, et al. Generalized chromomycosis caused by Phialophora verrucosa. Ann Dermatol Venereol. 2013;140:197-201.

"I shall either find a way or make one"

-Hannibal Barca

THE CLINICAL ACADEMIA