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

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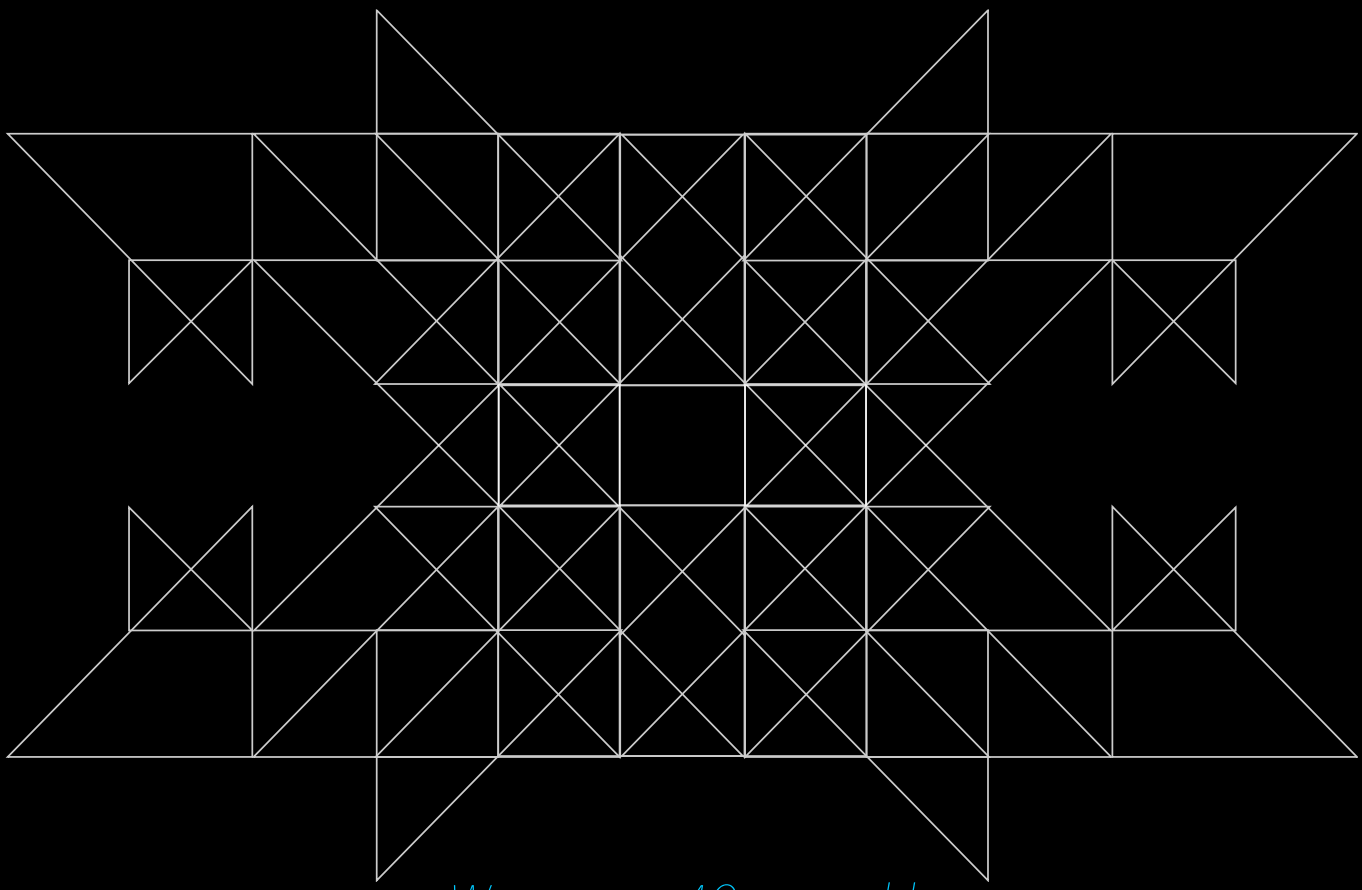

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Since the dawn of 2016, there have been many changes in our journal. There are things we want to do to improve our quality. Our passion is to bring out the best in every research presented in our journal and deliver properly to our audiences. The world of medicine is ever changing. Here now and then are its places. Keep going is the best suggestion for all of us. Hope you enjoy reading The Clinical Academia.

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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.
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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 overinterpret 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

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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.

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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.

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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.

Original Article

Student's learning outcomes of Integrated Patient-Centered Care Module

ORIGINAL ARTICLE BY

Sudarat Wijitsetthakul, M.D.
Ratchaburi Hospital, Ratchaburi, Thailand

ABSTRACT

OBJECTIVE
To evaluate the effects of integrated patient-centered care module (IPCCM) on medical students' learning outcomes in all three domains of knowledge, attitudes and skills.

METHODS
This is a quasi-experimental before and after study. A 5-day course of IPCCM was implemented to all 32 fifth year medical students at Ratchaburi Hospital in November 2015. This active learning module included flipped classroom, psychodrama, group discussion, peer teaching, role play with standardized patient, home visit and daily self-reflection that was facilitated by one main instructor using study guide. Their knowledge and attitudes were assessed before and after taking the module. Their skills were also determined at the end of the module. Thematic analysis was done for self-reflection analysis.

RESULTS
It found that learning outcomes of IPCCM regarding knowledge domain increased (paired mean difference, 29.7 ; 95% confidence interval (CI) 21.9 to 37.4; $P<0.001$), attitudes domain also increased (paired mean difference, 19.3 (95% CI 11.1 to 27.5; $P<0.001$). All students passed home visit and teamwork skills assessments with the scores of 93.0±3.1% and 89.7±3.6%, respectively. More than a quarter of the students reflected that their learning outcomes were better than taking the traditional classroom in all domains. Half of them satisfied with the study guide as they said it was very beneficial. All students reflected that their communication skills improved and appreciated this module as well as requested it to be continued.

CONCLUSION
A 5-day course of IPCCM improved all three domains of learning outcomes in fifth year medical students regarding knowledge and attitudes. It also had positive effect on students' skill regarding home visit and team work.

INTRODUCTION

Integrated curriculum is one of medical education strategies to promote learning outcomes regarding three domains of knowledge, attitudes and skills as well as clinical reasoning and problem solving skills. The integration can be divided into horizontal integration (interdisciplinary), vertical integration (problem-based) and spiral integration (theme-based or combination of both horizontal and vertical integration).[1-8] It allows students gain their knowledge in both basic and clinical sciences.[3] It also increases student's engagement and motivation.[8,9] However, it is resource-intensive and time consuming.[1,6]

Integrated curriculum was used to apply in patient-centered learning for the first and second year students in University of North Dakota School of Medicine and Health Sciences to promotes professionalism including the three domains of learning outcomes within two years.[11] This study aims to evaluate a shorter course with the application of integrated curriculum concept in a theme of patient-centered care or integrated patient-centered care module (IPCCM) in relation to the three domains of learning outcomes.

METHODS

Study design

This is a quasi-experimental before and after study determining the improvement of learning outcomes regarding the three domains of knowledge, attitudes and skills of IPCCM. Qualitative approach was also used for thematic analysis of students' reflection.

Participants

The participants were all 32 fifth year medical students at Medical Education Center, Ratchaburi Hospital, Thailand regardless of their gender, age and grade point average. The study was conducted in November 2015.

Teaching methods

We use various techniques of teaching of 5-day course of IPCCM (Table 1). All students were equipped with study guide as an manual for them during the module. The guide informed them objectives and teaching methods of all activities in the module. For psychodrama, it is often used as a psychotherapy but can also be applied to medical education especially for communication skills teaching. It focuses on two main actors: one student acts as a doctor, another acts as patient, and the remain students take role as directors facilitated by instructor. It offers a creative thinking for an individual and group to explore and solve the problems that improves skills domain.

Study procedure

On the first day, the student's knowledge and attitudes were evaluated by multiple choice questions (MCQs) and Likert scale questions (LSQs), respectively before class. Patient-centered medicine was the first topic coached by flipped classroom in the morning and psychodrama in the afternoon. The second day was about holistic care, flipped classroom was applied in the morning and small group discussion in the afternoon. Breaking bad news was on the third day instructed by peer teaching in the morning and role play with standardized patients was done in the afternoon. The fourth day topic was

Table 1. Teaching methods for integrated patient-centered care module

Teaching methods	Affected learning domain
Flipped classroom	Knowledge
Psychodrama	Skills regarding communication and teamwork
Group discussion	Skills for teamwork
Peer teaching	Knowledge via adult learning
Role play with standardized patients	Communication skills
Home visit	Knowledge, attitudes and skills
Daily self-reflection	Knowledge, attitudes, skills and profession developments

home visit, the students were divided into five groups. They discussed for their home health care plan and shared them with each other in the morning, and went to patients' homes with nurse practitioners coached in the afternoon (two to three students/coach/case). They were also assessed by nurse practitioners for their home visit skills. On the last day, the students were asked to present their results of their home visits to all instructors and their friends all day, teamwork assessment were performed by all instructors included one main instructor and five nurse practitioners. Posttest was done by all students at the end of the module. Self-reflection was done by everyone everyday which recorded for analysis on the last day.

Assessment tools

Four evaluation tools were used; (i) 8 multiple-choice questions (MCQs) for knowledge evaluation; its reliability using Cronbach's Alpha was 0.82, (ii) 10-point LSQs for attitudes evaluation; its reliability using Cronbach's Alpha was 0.85, (iii) analytic rubrics used for home visit and teamwork skills evaluation; reliability by Intra and inter observer reliability were 0.88 and 0.91 in home visit and teamwork skills evaluation, respectively and (iv) thematic analysis of students' reflection. The tools we used were verified their contents by three family physicians and three nurse practitioners at Ratchaburi Hospital. MCQs and LSQs were collected before and after the IPCCM. Analytic rubrics were determined at the end of the IPCCM. Student's self-reflection was recorded on last day (Figure 1).

Statistical analysis

Paired t-test was used to compare the mean scores (paired mean difference) regarding MCQs and LSQs, with their 95% confidence interval (CI). Mean score was used for analytic rubrics for evaluation of the students' skills, compared with minimal passing level (MPL) of 60%. Thematic analysis was done for self-reflection analysis.

Table 2. Characteristics of the students

Characteristic	Value (N=32)
Female sex-%	65.6
Age-yr	
Median	22.9
Interquartile range	22.8-23.3
Grade point average	3.1±0.3

Plus minus values are mean plus minus SD

RESULTS

All 32 fifth year medical students were included in the analysis. Mostly were female with the median age of nearly 23 years with relatively fair grade point average (Table 2). For their leaning outcomes, in the domain of knowledge, their scores increased significantly (paired mean difference, 29.7; 95% CI 21.9 to 37.4, P<0.001) (Table 3). In relation to the domain of attitudes, their scores increased from 62.4 to 81.7 (paired mean difference, 19.3%; 95% CI 11.1 to 27.5, P<0.001). For the skills domain, it revealed that mean home visit score was 93±3.1% and teamwork score was 89.7±3.6%. Both passed the MPL.

For thematic analysis of students' self-reflection on the last day of the module, it showed that 28.1% of the student reflected that their learning outcomes were better than taking the traditional classroom (2-week period in the fourth year) in all three domains, 50.0% of them satisfied with the study guide as they thought it was very beneficial. All students reflected that their communication skills improved and appreciated this module as well as requested it to be continued for the junior next class.

CONCLUSION

This five-day short course of integrated curriculum concept applied to IPCCM improved student's learning outcomes in all three domains including knowledge and attitudes. It also affected the students' skills regarding home visit and team work. The module was a spiral integration that mixed interdisciplinary and problem-based learning using multi-methods of teaching.

For patient-centered care, the students have to explore both diseases and illnesses of the patient, understand the whole person, find patient's common ground, incorporate prevention and health promotion, enhance the doctor-patient relationship, and make decision based on available resources. This allows students would construct all prior knowledge and skills in medicine both basic and clinical sciences to approach the patient professionally. In the present study, the students' knowledge was improved by using flipped classroom, group discussion and peer teaching. The improvement of their attitudes were promoted by using home visit and self-reflection. The skills domain of learning outcomes was also enhanced via psychodrama, group discussion and role play with standardized patient.

To our knowledge, this was the first study exploring the effects of integrated curriculum in a short course. As the IPCCM was a short course, thus, the improvement of students' knowledge, attitudes

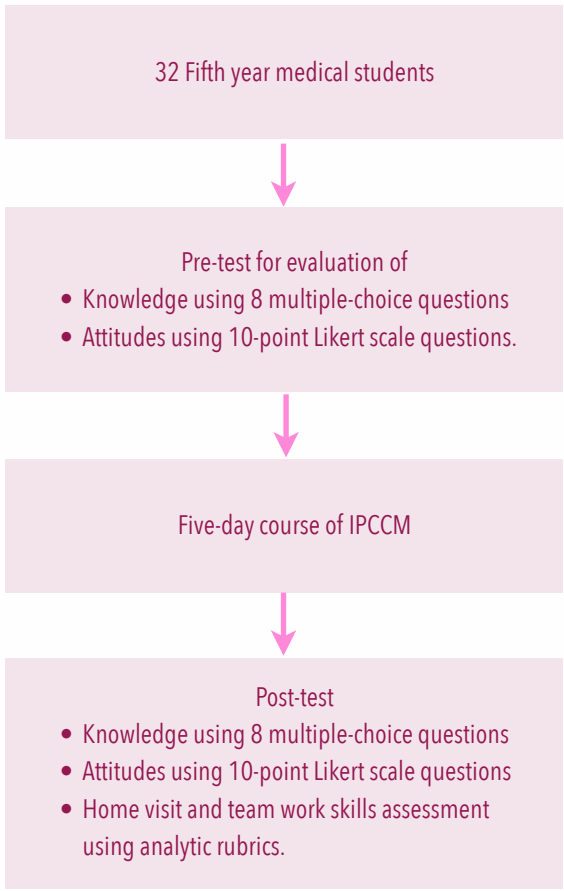

Figure 1. Study flow regarding Integrated Patient-Centered Care Module (IPCCM) and learning outcomes evaluation.
A 5-day course of IPCCM was implemented to all 32 fifth year medical students. They were divided into three rotation in two weeks. Multiple-choice questions (MCQs) for knowledge evaluation and 10-point Likert scale questions (LSQs) for attitudes assessment were done before the module. MCQs and LSQs were used again on the last day of the module as well as home visit and teamwork skills evaluation were done using analytic rubrics.

and skills would have minimal influences from outside contaminations and co-interventions. However, the module had only one main instructor with five nurse practitioners, this might be problem with generalizability of the findings to other settings. Moreover, the effects of IPCCM in the present study were concluded based on only 32 students. Larger study with better design should be conducted.

In our study, the study guide helped they achieved the learning objectives. The results of immediate effects on learning outcomes were consistent with previous studies of the integrated curriculum.[1-9] The content knowledge in relation to clinical reasoning and problem solving skills of students in Fatima Jinnah Medical College for Women, Lahore improved.[4] The study from Erasmus MC Medical School, Rotterdam, the Netherlands

Table 3. Learning outcomes in the three domains

Domain	Pre-test	Post-test	Paired mean difference (95% confidence interval)
	Mean score±standard deviation		
Knowledge	52.6±16.5	82.3±13.3	29.7 (21.9-37.4)
Attitudes	62.4±13.0	81.7±6.7	19.3 (11.1-27.5)
Skills			
Home visit	-	93.0±3.1	-
Teamwork	-	89.7±3.6	-

showed that the benefit of a short integrated program in five-week improved knowledge of students at risk.[10] This might indicate positive effects of student's professionalism using patient-centered care on patients' perceptions and wellness. [11-13]

In conclusion, IPCCM was found to be beneficial for students learning outcomes, it also resource-intensive and time consuming as there was only one instructor. With limitation regarding sample size and study design. A cluster randomization with larger number of participants should be conducted. Further module development might recruit other health professions for more nurse practitioners, pharmacists, physical therapists or public health volunteers for better interdisciplinary approach.

ACKNOWLEDGMENTS & DECLARATION

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COMPETING INTERESTS: This study has no competing of interests.

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Pterygium size and risk of recurrence in patient undergoing pterygium excision with amniotic membrane transplantation

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To assess the association between pterygium size and risk of recurrence after pterygium excision with amniotic membrane transplantation (AMT)

METHODS

We performed a cohort study of patients who underwent pterygium excision with AMT at Surin Hospital from June 1, 2014 to May 31, 2015. The primary outcome was recurrence pterygium (Grade IV) at 6 months after the surgery. Secondary outcomes included complications after excision with AMT.

RESULTS

Of 143 patients were enrolled. Three (2.1%) had previous history of pterygium excision. After 6 months of follow up, the incidence of recurrence for primary, recurrent, and all pterygium was 24.3%, 100%, 25.9% respectively. In multivariate analysis, patients who had pterygium limbal size larger than 5.5 mm, as compared with those had lesser or equal than 5.5mm had an adjusted relative risk (RR) of recurrence pterygium of 3.97 (95% confidence interval (CI), 1.04 to 15.16; P=0.04). Moreover, previous history of pterygium excision and ophthalmologist's experience were also associated with an increased risk of recurrence. (adjusted RR, 4.20; 95% CI, 1.35 to 13.05; P=0.01; adjusted RR, 11.8; 95% CI, 2.61 to 53.29; P=0.01, respectively).

CONCLUSION

Larger than 5.5 mm pterygium limbal size was associated with an increased recurrent risk of those with pterygium excision with AMT at 6 month after surgery.

INTRODUCTION

Pterygium is a winglike fibrovascular tissue and currently is considered as an abnormal growth disorder rather than degenerative disorder.[1-2] There are several surgical techniques for pterygium excision to prevent recurrence.[3-11] The surgical techniques for pterygium excision include conjunctival autograft, limbal autograft and amniotic membrane transplantation (AMT) using adjuvant therapies such as beta radiation, thiotepa, mitomycin C, 5-fluorouracil and daunorubicin. The limbal autograft technique is the most effective way of reducing recurrence but it needs surgical experience and time consuming. Conjunctival autograft is the second most effective means of technique but limited in double headed pterygium or advance pterygium.[4,5,12] Combination of conjunctival or limbal autograft with adjuvants reduces the pterygium recurrence. Using adjuvant therapies are associated with delayed conjunctival epithelialization, keratitis, scleral ulceration, glaucoma and endophthalmitis. Therefore, AMT is the alternative choice with easier technique and less complication.

Even though various technique have been employed with pterygium excision, recurrence still remains.[6,13-14] Well-known risks of recurrence include young age and sun exposure time.[15-17] In a previous study, it showed that fleshiness of the pterygium was associated with increase in recurrence in bare sclera technique.[18-19] Few studies focused on risk factors for the development of recurrence in pterygium excision with conjunctival graft.[20-23] From an image analysis study, it found that pterygiam size and area were associated with recurrence in univariate analysis.[24] But there was no significant difference in recurrence between pterygia wide base and narrow base in the two previous studies by Torres-Gimeno A et study and Varssano D et study.[21,23] Similarly, Prabhasawat et al reported pterygia tissue removal were not related to time to recurrence.[4] However, risk factors especially the pterygium size for recurrent after pterygium excision with AMT has never been reported. We, hence, conducted the present study to evaluate the association between pterygium size and risk of recurrence in patients with pterygium excision with AMT.

METHODS

Study design and oversight

This was a prospective cohort study of patients undergoing pterygium excision with AMT. The study was approved by Research Ethics Committee, Surin Hospital with the reference number of 12/2557. All participants gave written informed consent.

Participants and study site

All patients underwent pterygium excision with AMT at Surin Hospital from June 1, 2014 to May 31, 2015 were enrolled. We excluded those whom undergone double headed pterygia or bilateral pterygium excision.

Data collection

The patients were examined randomly by 5 ophthalmologists. The decision of pterygium excision was made independently by each doctor. Patient

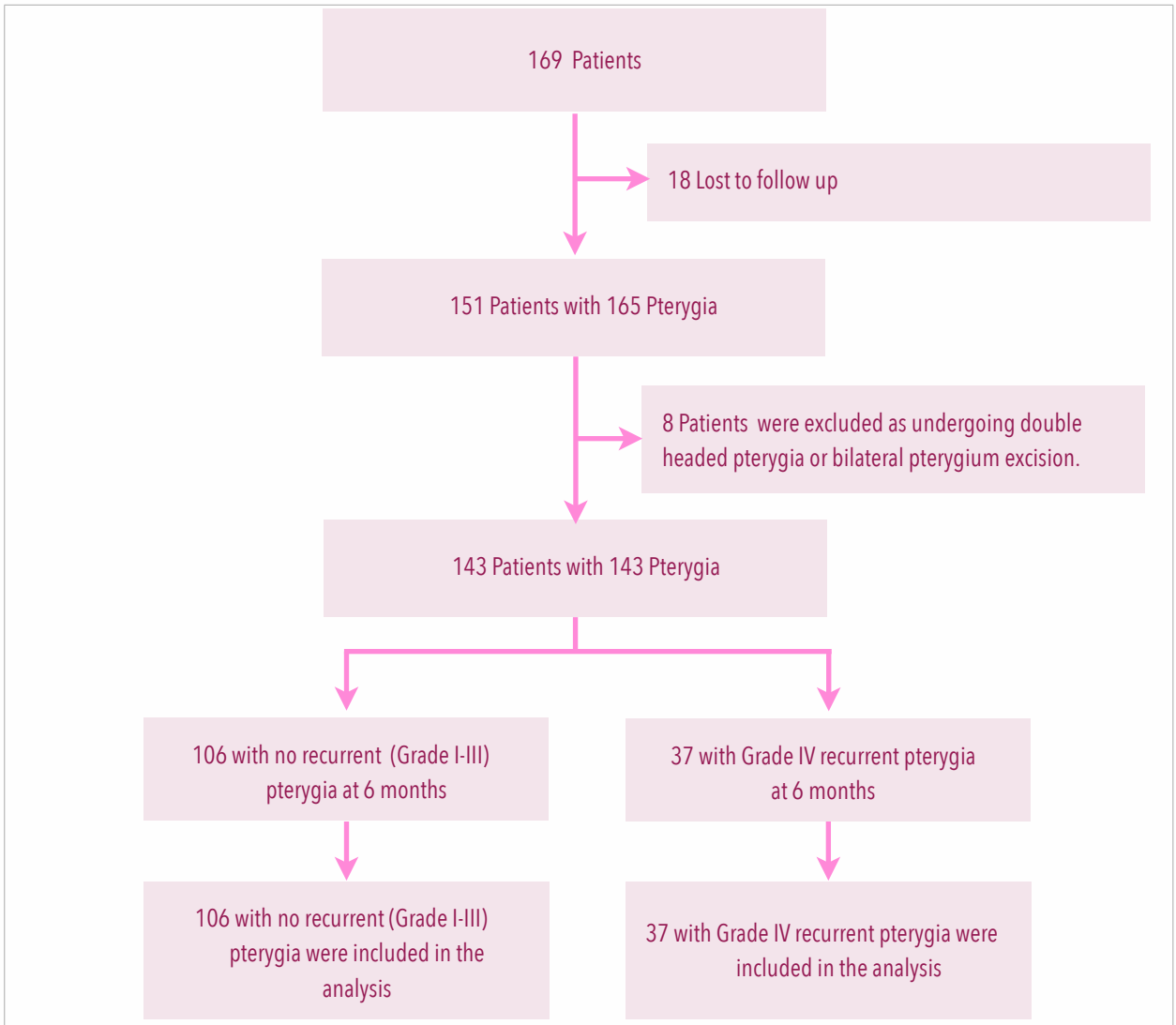

Figure 1. Flow of the study

baseline characteristics data included age, sex, occupation, daily sun exposure time, underlying diseases and history of pterygium excision. Pterygium side, morphology of pterygium, pterygium size (limbal and radial size), suture material and years of experience of ophthalmologists were also collected. Morphology of pterygium based on fleshiness of pterygium. Morphology pterygium grading was classified into 3 grades. The morphology grading was based on the criteria given by Tan DT.[18] Grade I (atrophic pterygium) is pterygium that has episcleral vessels under body of pterygium seen clearly. Grade II (intermediate pterygium) is partially obscured. Grade III (fleshy pterygium) is pterygium that episcleral vessels is totally obscured by body of pterygium. Pterygium size was measured by caliper

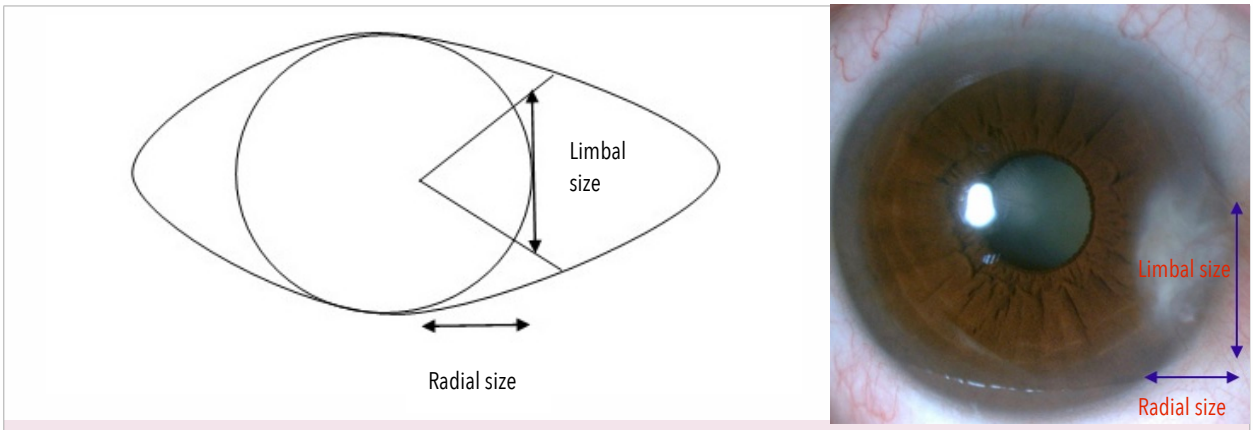

Figure 2. Measuring pterygium size; limbal and radial size

in vertical (limbal size) and horizontal (radial size) dimension at limbus (Figure 2). The measurement was done independently by individual ophthalmologist.

After the surgery, patients received postoperative medications for 2 months, based on ophthalmologist own preferences. The treatment option could be classified into 3 groups. Group I is topical 0.1% dexamethasone phosphate (Seng Thai Medical, Bangkok, Thailand) 4 times a day and tear film lubricants. Group 2 is topical 0.1% dexamethasone phosphate 4 times a day, oral indomethacin 3 times a day for first 5 days and tear film lubricants. Group 3 is topical 1% prednisolone acetate (Seng Thai Medical, Bangkok, Thailand) every 2 hours in first month then 4 times a day for one month, nightly maxitrol (neomycin sulfate 3500 units/g, polymyxin B sulfate 6000 units/g, dexamethasone 0.1%) ointment (Alcon, Belgium) for one month and poly-oph (Seng Thai Medical, Bangkok, Thailand) 4 times a day. Patients were then followed at 1 week, 2 week, 1 month, 2 months and 6 months. Complications included recurrence, malapposition of amniotic graft, conjunctival granuloma, steroid induce glaucoma were evaluated at each visit. Recurrence grading was defined by criteria given by Prabhasawat et al.[4] Grade I is that surgical area was similar as normal appearance. Grade II is that there were only fine episcleral vessels in the surgical area between limbus and conjunctiva. Grade III is that there were fibrovascular tissues in surgical not involved limbus. Grade IV is that there were fibrovascular tissues invading the cornea.

Outcomes

The primary outcome was recurrence at the 6-month follow up visit. Recurrence was defined as recurrence grade IV. The other grades were defined as non-recurrence. The secondary outcomes were complications including malapossition, conjunctival granuloma, steroid induced glaucoma and persistent epithelial defect.

Statistical analysis

For descriptive statistics, mean and standard deviation were used for normal distributed

Table 1. Characteristics of the patients and their pterygia

Characteristics	Value
Patients and pterygia (n=143)	
Age-yr	58.0±11.3
Female sex-no. (%)	102 (71.3)
History of recurrent pterygium-no. (%)	3 (2.1)
Daily of sun exposure time-hr	4.4±2.3
Hypertension-no. (%)	22 (15.4)
Diabetes-no. (%)	4 (2.8)
Using simvastatin as a medication	8 (5.6)
Occupation-no. (%)	
Farmer	97 (68.3)
Government officer	12 (8.5)
Others	34 (23.2)
Primary pterygium-no. (%)	140 (97.9)
Nasal side-no. (%)	130 (90.9)
Morphology of pterygium before surgery-no.(%)	
Grade I	8 (5.8)
Grade II	72 (51.8)
Grade III	59 (42.4)
Limbal size-mm	6.7±1.8
Radial size-mm	5.0±1.5

Plus minus values are mean plus minus standard deviation

Table 2. Outcomes of the treatment

Outcome	No. (%)
Recurrence within 6 months	
Grade I	26 (18.2)
Grade II	24 (16.8)
Grade III	56 (39.1)
Grade IV	37 (25.9)
Malapposition	12 (8.4)
Conjunctival granuloma	4 (2.8)
Steroid induced glaucoma	14 (9.8)
Persistent epithelial defect	1 (0.7)

continuous variable and number with percentage were used to summarized categorical variables. We also calculated crude relative risk (RR) for each factor that might associate with recurrent pterygium at 6 months by using Generalized Estimating Equation (GEE) method. The univariate analysis was firstly performed for variables regarding age, sex, daily sun exposure time, underlying disease, history of pterygium excision, pterygium side, morphology of pterygium, pterygium size (limbal and radial size) experience of the ophthalmologist and medication to explore potential factors that associated with the recurrence at 6-month. All variables that showed $P<0.10$ from the univariate analysis and variables (age and sun exposure time) which have been reported to be potential confounders were then selected to include in the GEE method to assess risk factors to recurrence at the 6-month follow up visit to calculate adjusted RR. The analyses were performed using SPSS Statistics software, version 20.

RESULTS

Among 143 patients enrolled, the mean age of the patients was 58.0 years. Three patients (2.1%) had previous history of pterygium excision. Loss to follow up at 6 months was 10.7 % (Figure 1). Baseline characteristics of patients and their pterygia are shown in Table 1.

Of a total of 143 pterygia removed, 130 were nasal sides and 13 were temporal sides. The majority of pterygium (65%) was in Grade III and IV. The mean pterygium limbal size was 6.7 mm and the mean radial size was 5.0 mm. All surgeries were performed by five ophthalmologists; two with experiences of 3 years or longer and three with experiences shorter than 3 years. An 8-0 vicryl was used as suture material in 99.4% of all patients. After 6 months of follow up, 24 pterygia (16.8%) had recurrence Grade II, 56 (39.1%) had recurrence Grade

Table 3. Factors associated with Grade IV recurrent pterygium in 6 months after excision with amniotic membrane transplantation

Factors	No recurrence in 6 months	Grade IV recurrence in 6 months	Crude relative risk (95% confidence interval)	Adjusted relative risk (95% confidence interval)
Age group-yr				
20-40	8 (7.6)	1 (2.7)	Reference	
41-60	49 (46.2)	19 (51.4)	2.51 (0.38-16.60)	2.14 (0.39-11.78)
61 or older	49 (46.2)	17 (45.9)	2.32 (0.35-15.37)	2.10 (0.38-11.62)
Female-no. (%)	76 (71.7)	26 (70.3)	0.95 (0.52-1.74)	-
Daily sun exposure time-hr	4.4±2.4	4.5±2.1	1.02 (0.91-1.14)	0.98 (0.87-1.10)
Hypertension-no. (%)	20 (18.9)	2 (5.4)	0.31 (0.08-1.22)	0.52 (0.13-2.05)
Diabetes-no. (%)	2 (1.9)	2 (5.4)	2.00 (0.71-5.51)	-
Using simvastatin as a medication-no. (%)	6 (5.7)	2 (5.4)	0.96 (0.28-3.31)	-
History of recurrent pterygium-no. (%)	0	3 (8.1)	4.12 (3.08-5.51)	4.20 (1.35-13.05)
Nasal side-no. (%)	95 (89.6)	35 (94.6)	1.75 (0.48-6.34)	
Morphology of pterygium before surgery-no. (%)				
Grade I	6 (5.7)	2 (5.9)	Reference	
Grade II	59 (56.2)	13 (38.2)	0.72 (0.20-2.65)	
Grade III	40 (38.1)	19 (55.9)	1.29 (0.37-4.51)	
Limbal size larger than 5.5 mm-no. (%)	72 (68.6)	32 (94.1)	5.38 (1.36-21.35)	3.97 (1.04-15.16)
Radial size larger than 5.5 mm-no. (%)	31 (29.2)	19 (55.9)	2.28 (1.26-4.11)	1.52 (0.82-2.84)
Experience of doctor shorter than 3 years-no. (%)	52 (49.1)	34 (91.9)	7.51 (2.42-23.33)	11.80 (2.61-53.29)
Post-operative treatment-no. (%)				
Topical steroid	61 (57.5)	18 (48.6)	Reference	
Topical steroid with oral NSAIDs	27 (25.5)	2 (5.4)	0.30 (0.07-1.23)	3.17 (0.46-21.80)
High frequency topical steroid	18 (17.0)	17 (45.9)	2.13 (1.26-3.61)	0.97 (0.54-1.73)

Plus minus values are mean plus minus standard deviation; NSAIDs=non-steroidal anti-inflammatory drugs

III and 37 (25.9%) had recurrence Grade IV. The incidence of recurrence was 24.3% in primary pterygium and was 100% in recurrent pterygium. Complications after the surgery included 12 patients with malappositions, 4 patients with conjunctival granuloma, 14 patients with steroid induce glaucoma and 1 patient with persistent epithelial defect (Table 2).

For identifying factors associated with recurrent pterygium, from univariate analysis, previous history of pterygium excision, hypertension, pterygium size (limbal and radial size), ophthalmologist's experience and high frequency topical steroid were associated with an increased risk of recurrence pterygium at $P<0.1$. However, only three factors showed significant at $P<0.05$ in the multivariate analysis; recurrence pterygium was found higher in those with pterygium limbal size larger than 5.5 mm (adjusted RR 3.97; 95% CI, 1.04 to 15.16; P=0.04), previous history of recurrent pterygium (adjusted RR, 4.20; 95% CI, 1.35 to 13.05; P=0.01), and ophthalmologists with experience shorter than 3 years (adjusted RR, 11.80; 95% CI 2.61-53.29; P=0.01). Difference in post-operative treatment was not significantly associated with the risk of recurrence (Table 3).

DISCUSSION

In this prospective cohort study, of patients with pterygium who received excision with amniotic membrane transplantation we found 25.9% of recurrence. The study showed that larger pterygium limbal size more than 5.5 mm, previous history of pterygium excision and less surgical experience ophthalmologist resulted in a significantly higher rate of recurrence pterygium.

Prabhasawat et al reported on a series of cases in United States in which the recurrence rate was 10.9%, 37.5%, 14.8% for primary, recurrent, and all pterygium respectively.[4] The recurrence that we observed in our cohort was higher than this study but was similar to the result of study in Thailand by Luanratanakorn P. et al.[5] This could be explained by difference in race, sun exposure time of the patients. Our patients were mainly farmers in the tropical area, thus, they had high opportunity to expose to the sun compared with patients observed in other studies.

We found recurrent rate was greatly in recurrent pterygia. These findings were similar in other studies.[4,5,17] The recurrent pterygia have more intensive fibrovascular tissue and performing in these cases is challenging. In previous studies showed young age, fleshiness of the pterygium and sun exposure as significant risk factor for recurrence of pterygium.[15-19] However, those factors showed no statistically significant association with recurrence pterygium in our study. Torres-Gimeno A et al reported that male, high sun exposure time but not pterygium limbal size were associated with an increased risk of recurrence.[23] Han SB et al demonstrated relative size and relative area were significantly related recurrence in univariate analysis but only degree of vascularity were associated with recurrence in multivariate analysis.[24] However, in this study we found a relative risk of 3.97 among pterygium limbal size larger than 5.5 mm group as compared with pterygium limbal size 5.5 mm or lesser group. The cut-off pterygium limbal size was based on significance in both univariate and

multivariate analysis. We hypothesized that larger pterygium limbal size possesses greater of fibrovascular tissue which potentially increase postoperative ocular surface inflammation and play role in recurrence. These results suggested that pterygium limbal size should be one of a considering factor for early pterygium excision with AMT graft. Surgical technique is dominant factor in the risk of recurrence.[6,25] Wide excision of fibrovascular tissue as much as possible and well-secured amniotic graft decrease the recurrence.[13-14] We found less doctor experience was associated with high recurrence. It can be due to difficulty in adequately excision subtenon.

The strength of this study is prospective cohort study design to evaluate risk factors that has larger sample sizes than other studies. However, the limitation of this study includes selection of the patient and measurement bias. There was the different characterization of the patients who received surgery by ophthalmologists. However, our additional analysis showed that patients who received surgery by ophthalmologists with long or short experience were significantly different in only two variables. Firstly, the size of pterygia performed by ophthalmologists with lesser experience was larger than that performed by long experience ophthalmologist. But this significance was not clinically significant (difference 0.8 millimeters in limbal size and 0.72 millimeters in radial size). Secondly, among lesser doctor's experience group, patients reported of using more simvastatin. Simvastatin has anti-inflammatory effects which may have impact on reducing recurrence, as compared with other hypocholesterolemic activity.[26] Nevertheless, using simvastatin was not found to be a protective factor of recurrence in this study population.

In our study, morphology pterygium grading and size measurement was done by individual ophthalmologist. Interrater variability might be decreased by assessment with the same investigator.However, the size measurement was done by simple procedure and the result was adjusted for experience of ophthalmologist so bias should be small. Another limitation is that our method of estimating daily sun exposure time used interrogation. It was recalled by patients and maybe inaccurate. Finally, because 68.3% of the patients were farmer, our results may not apply to office worker.

In conclusion, larger than 5.5 mm pterygium limbal size was associated with higher risk of recurrence pterygium after pterygium excision with AMT. Our data suggested that pterygium limbal size should be taken into consideration before surgery. Further research with larger limbal size in larger sample is needed.

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COMPETING INTERESTS: This study has no competing of interests.

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Adverse effects of crystalloids versus colloids for fluid resuscitation in dengue shock syndrome: systematic review

ORIGINAL ARTICLE BY

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ABSTRACT

OBJECTIVE

To synthesize the evidence to identify adverse effects of crystalloids and colloids for intravenous fluid resuscitation in patients with dengue shock syndrome (DSS).

METHODS

This is a systematic review to assess the adverse effects of crystalloid and colloid solutions for fluid resuscitation in DSS. We searched electronically through five online databases from Pubmed, SCOPUS, Cochrane library, ScienceDirect and Ovid with no language restrictions. All the reference sections of all studies were reviewed to identified relevant studies to identify all relevant randomized controlled trials (RCT) comparing colloid and crystalloid solutions for intravenous infusion of those with DSS.

RESULTS

Allergic reaction after infusion of crystalloids was lower compared with that of colloids (0% vs 4.4%; RR 0.08, 95 % CI, 0.01 to 0.62; P=0.02; I^2=0%). However, no significance differences regarding incidence of bleeding and requirement of diuretics were observed; the RR of new bleeding was 0.89 (95% CI, 0.57 to 1.40; P=0.62; I^2=0%); 8.4% in children receiving crystalloids and 13.5% in children receiving colloids. The rate of requiring for diuretic was similar between the two interventions (18.8% vs 26.1%; RR, 0.90; 95% CI, 0.45 to 1.78; P=0.76 I^2=73%. In one subgroup analysis with 2 RCTs of new bleeding comparing between lactated Ringer's solution and dextran, the rates of new bleeding were also similar between the two interventions (10.9% vs 13.3%; RR, 0.92; 95% CI, 0.55 to 1.52; P=0.74; I^2=0%).

CONCLUSION

Allergic reaction was more common in those with colloid solution. There were no differences in term of new bleeding and requirement of diuretics for children with DSS receiving either colloid or crystalloid solution.

INTRODUCTION

Dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) are major causes of childhood morbidity and mortality in many tropical countries.[1] The disease is a major public health concern in South and Southeast Asia, the Western Pacific, and Central and South America and is now being reported in other tropical regions.[2] DHF is characterized by an increase in capillary permeability and haemostatic changes.[3] It caused by any one of four serotypes of dengue virus (DENV).[4] DSS is a severe form of DHF with hypotension caused by severe plasma leakage leading to DSS that featured by cold blotchy skin, circumoral cyanosis, and circulatory disturbances. Acute abdominal pain and persisting vomiting are early warning signs of impending.[3,5] There are 200,000 to 500,000 cases of potential life-threatening DHF and DSS that are reported to the World Health Organization (WHO).[6,7] The death rate associated with the more severe form DHF and DSS is approximately 5%, predominantly in children under the age of 15.[5,6] For patients with DSS, the WHO recommends immediate volume replacement with isotonic crystalloid solutions, followed by the use of plasma or colloid solutions (specifically, dextran) for profound or continuing shock.[8]

For many years there has been controversy over whether crystalloid or colloid solutions should be used for volume replacement in the treatment of shock.[8] There were 3 randomized controlled trials (RCTs) conducting in Vietnam comparing crystalloids versus colloids as intravenous resuscitation in children with DSS but only two RCTs can detect clinically important adverse effects.[9] The first pilot RCT was conducted in 1999 in 50 patients with administration of four fluid types; 0.9% saline, lactated Ringer's solution, gelafundin and dextran. It seemed that colloid solution was superior over crystalloid solution in relation to mean hematocrit, systolic blood pressure, pulse pressure and cardiac index value.[1] The second RCT in 2001 with 222 patients confirmed the benefit of colloid over crystalloid solution in children presenting with a pulse pressure of lower than 10 mmHg regarding median pulse pressure recovery time and the proportion whose recovery time was more than one hour.[8] The final RCT in 2005 with 512 children stated the superiority of colloid over crystalloid solution in term of median reduction of the hematocrit in two hours after study entry.[6] However, the adverse effect were reported fairly low in the three studies.[1,6,8] Nonetheless, their sample sizes were less likely to be adequate to test the hypothesis of whether colloid or crystalloid solution would be benefits for children with DSS. There have been no large-scale studies carried out to determine the optimal fluid regimen, and the current WHO guidelines have remained virtually unchanged. Largely as a result of the ongoing debates over whether crystalloids or colloids should be used for volume resuscitation in DSS.[8] This review we focused to synthesize the evidence to identify adverse effects of crystalloids and colloids for intravenous fluid resuscitation in patients with DSS

METHODS

Study design

This is a systematic review to assess the adverse effects of crystalloid and colloid solution for fluid resuscitation in DSS.

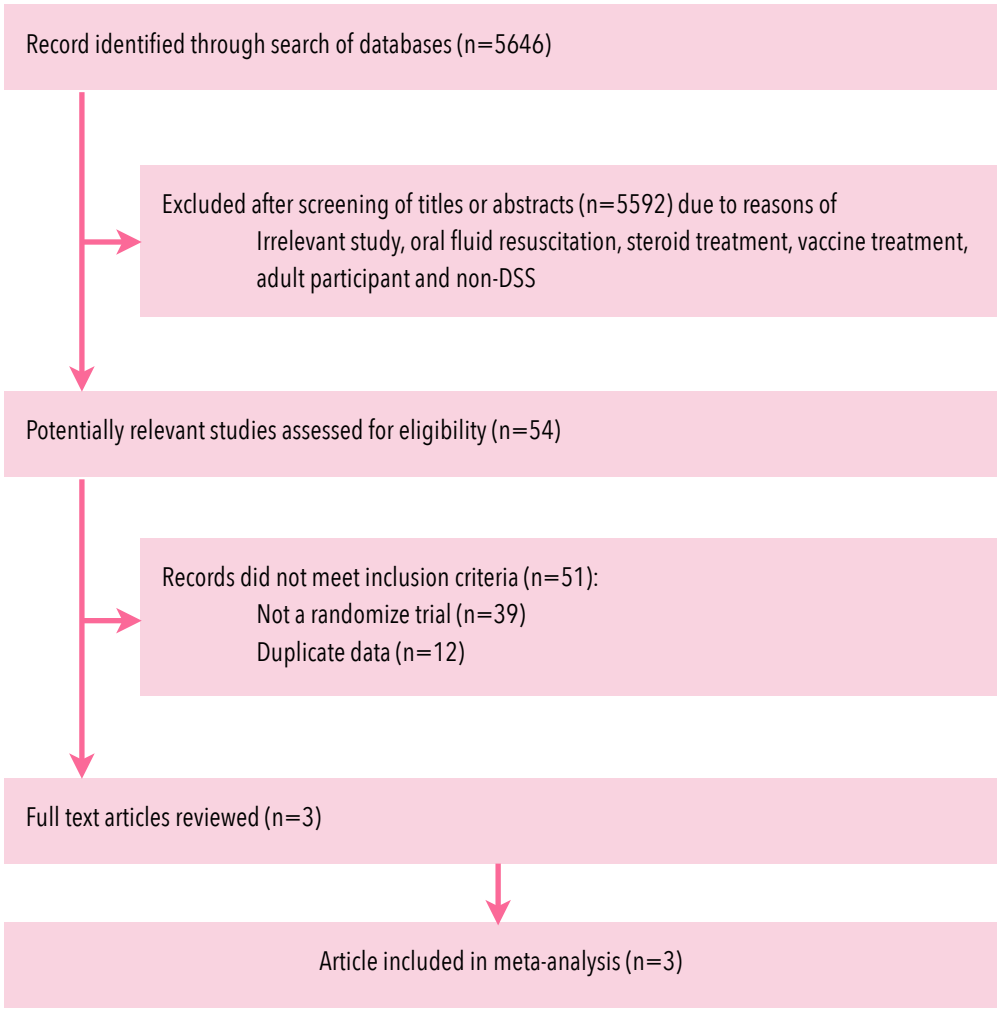

Figure 1. Summary of trials on fluid resuscitation in children retrieved from searches

Search strategy for identify relevant studies

We searched electronically through five online databases from Pubmed, SCOPUS, Cochrane library, ScienceDirect and Ovid up to September 2015 using keywords with Major Subject Heading (MeSH) strategies where appropriate of "dengue" and the other indexing is "fluid therapy" There were no limits or filter placed on searches, to get maximal sensitivity with no language restrictions. All the reference sections of all studies were reviewed to identified relevant studies by hand searching for unpublished study as well as gray literatures.

Inclusion criteria

We included only RCT that comparing any types of crystalloid and colloid solutions regardless to

Table1. Quality Assessment Based on Jadad Score

Question	Dung[1] 1999	Nhan[8] 2001	Wills[6] 2005
Was the study described as random?	1	1	1
Was the randomization scheme described and appropriate?	0	0	1
Was the study described as double-blind?	1	1	1
Was the method of double blinding appropriate?	1	1	1
Was there a description of dropouts and withdrawals?	1	1	1
Total score	4	4	5
Quality Assessment	High	High	High

1 = Yes, 0 = No; score 0 to 2, low quality; score 3 to 5, high quality

adverse outcomes to be included in our meta-analysis

Review methods and selection criteria

Two reviewers independently screened all titles and abstracts restriction to participants' characteristics including age (not younger than 15 years), diagnosed as dengue shock syndrome (Grade III and IV regarding WHO classification), no prior treatment with fluid resuscitation (Figure 1). Later, we excluded those that were non-RCTs, the fluid at least one comparison of crystalloid versus colloid.

Quality assessment of the included studies

The two investigators independently assessed the methodological quality of the selected studies by using the Jadad score. Thus we assessed in five term that firstly; the study was described as random, secondly; the randomization scheme was described and its appropriateness, thirdly; the study was described as double-blind, fourthly; the method was double blinding appropriately, and lastly; there was a description of dropouts and withdrawals (Table 1). If we assessed into 'Yes' , then give a one score for that term. The maximum score is five; more than or three score are high quality study.

Data abstraction

For each trial, we collecting information on the author's name, year of publication, country where the study was conducted, study design (randomization, allocation and masking), number of participants, number and percentage of a boys, fluid interventions given, outcome measures used, adverse effects of fluid interventions and mortality.

Data synthesis

We reported the benefit of crystalloid versus colloid in DSS in relation to allergic reaction after infusion,

Table 2. Characteristics of Studies Included in Meta-Analysis

Characteristic	Dung[1] 1999	Nhan[8] 2001	Wills[6] 2005
Participants – no.	50	222	512
Age – years	5 – 15	2 -15	2-15
Male sex – no. (%)	33 (66.0)	94 (42.3)	255 (49.8)
Place	The Pediatric Intensive Care Unit at the Centre for Tropical Diseases, Ho Chi Minh City, Vietnam	The ICU of Dong Nai Pediatric Hospital, in southern Vietnam	The Pediatric Intensive Care Unit at the Centre for Tropical Diseases, Ho Chi Minh City, Vietnam
Admission time	July to November 1995	September 1996 to September 1997	August 1999 to March 2004
Study design	Double blind, randomized controlled trial	Double blind, randomized controlled trial	Double blind, randomized controlled trial
Intervention	Ringer's lactate(n=13), Dextran70(n=12), gelafundin or gelatin (n=13), 0.9% saline (n=12) Bolus 20ml/kg over1 hour,10ml/kg over 2nd hour	Ringer's lactate(n=55), Dextran70 (n=55), Gelatin (n=56), Normal saline (n=56) Bolus 20ml/kg over1 hour, 10 ml/kg over 2nd hour	Ringer's lactate(n=128), 6% dextran 70(n=193), 6% hydroxyeyhyl starch (n=191) Group 1 = (moderate shock: pulsepressure >10 and ≤ 20 mm Hg) Dextran, starch, or Lactated Ringers. Group 2 = (severe shock: pulse pressure <10 mm Hg) allocated to Dextran or starch and given 15ml/kg over1 hour,10ml/kg over 2nd hour
Diagnosis of DSS	WHO guideline for Diagnosis with laboratory investigation	WHO guideline for Diagnosis with laboratory investigation	WHO guideline for Diagnosis with laboratory investigation
Primary outcomes	PP*(mmHg), PR* (beat per minute), BP* (mmHg), No. episode of shock, Hour in shock, Platelets, WBC, Reticulocyte	The initial PP* recovery time(from IV fluid therapy until PP>30 mmHg), PPRT†>1 hr, Reshock rate	Supplemental intervention with rescue colloid, Any rescue colloid, Rescue colloid for initial resuscitation no.(%), Rescue colloid required subsequently no.(%)
Secondary outcomes	Cardiac index (CO/BSA), Hematocrit (%), Further of crystalloid and colloid infusion(ml)	Decrease in hematocrit (%) and pulse (beat per minute) at 1 hour, Total volume of intravenous fluid infuse (ml/kg), Requirement(no% of patient) and volume (ml/kg) of dextran after first hour, Required furosemide (no% of patient)	Time to CVS stable(hour), Time to CVS sustain stable(hour) without any intervention, Volume of rescue colloid, total parenteral fluid (ml/kg), Percentage reduction of Hematocrit at 2 hr, Number of day in hospital
Adverse effects	Fluid overload and Pulmonary edema	Allergic reaction, Reshock ,Severe epistaxis, A large of hematoma at a site of minor trauma	Diuretic therapy no.(%), New bleeding after study entry, Clinical fluid overload, Volume of ascites

*PP = Pulse pressure, PR = pluse rate, BP = blood pressure, CO/BSA = cardiac output / body surface area

†PPRT = pulse pressure recovery time.

Study	Event/Total Crystalloids	Event/Total Colloids	Risk ratio,Mental-Haenszel,random(95%CI)	Risk ratio,Mental-Haenszel,random (95%CI)
Allergic reaction after infusion				
Nhan 2001	0/111	6/111		0.08 [0.00 to 1.35]
Wills 2005	0/128	16/384		0.09 [0.01 to 1.50]
Total (95% CI)	0/239	22/495		0.08 [0.01 to 0.62]
Test for Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%				
Test for overall effect: Z = 2.43 (P = 0.02)				
New bleeding after study				
Nhan 2001	0/111	2/111		0.20 [0.01 to 4.12]
Wills 2005	20/128	65/384		0.92 [0.58 to 1.46]
Total (95% CI)	20/239	67/495		0.89 [0.57 to 1.40]
Test for Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.32); I² = 0%				
Test for overall effect: Z = 0.49 (P = 0.62)				
Required diuretic (furosemide)				
Nhan 2001	20/111	15/111		1.33 [0.72 to 2.47]
Wills 2005	25/128	114/384		0.66 [0.45 to 0.97]
Total (95% CI)	45/239	129/495		0.90 [0.45 to 1.78]
Test for Heterogeneity: Tau² = 0.18; Chi² = 3.64, df = 1 (P = 0.06); I² = 73%			0.01 0.1 1 10 100 Favorus crystalloid Favorus colloid	
Test for overall effect: Z = 0.31 (P = 0.76)				

Figure 2. Comparison the effects of crystalloid and colloid solutions

Study	Event/Total LR	Event/Total Dextran	Risk ratio,Mental Haenszel,random (95%CI)	Risk ratio,Mental Haenszel,random (95%CI)
Nhan 2001	0/55	1/55		0.33 [0.1 to 8.01]
Wills 2005	20/128	32/139		0.94 [0.56 to 1.57]
Total (95% CI)	20/183	33/248		0.92 [0.55 to 1.52]
Test for Heterogeneity: Tau² = 0.00; Chi² = 0.40, df = 1 (P = 0.53); I² = 0%			0.01 0.1 1 10 100 Favorus crystalloid Favorus colloid	
Test for overall effect: Z = 0.33 (P = 0.74)				

Figure 3. Comparing new bleeding after study of lactated Ringer's solution (LR) and dextran

Study	Event/Total Crystalloid	Event/Total Colloid	Risk ratio,Mental Haenszel,random (95%CI)	Risk ratio,Mental Haenszel,random (95%CI)
Pulse pressure recovery time (PPRT) more than 1 hr.				
Nhan 2001	15/111	6/111		2.50 [1.01 to 6.21]
Test for overall effect: Z = 1.97 (P = 0.05)				
Re-shock rate of patients				
Nhan 2001	32/111	31/111		1.03 [0.68 to 1.57]
Test for overall effect: Z = 0.15 (P = 0.88)				
Rescue colloid for initial resuscitation				
Wills 2005	4/128	14/384		0.86 [0.29 to 2.56]
Test for overall effect: Z = 0.28 (P = 0.78)			0.01 0.1 1 10 100 Favorus crystalloid Favorus colloid	

Figure 4. Outcomes based on one study comparison the effects of crystalloid and colloid solutions

new bleeding after study, required diuretic (furosemide), and subgroup analysis in new bleeding after studies of lactated Ringer's solution and dextran. For the dichotomous outcomes we used the relative risk with a random effect model. Data analysis was performed by Revman5 software developed by The Cochrane Collaboration. Heterogeneity was assessed by I^2 statistics. Random effect model meta-analysis was used to estimate risk ratio (RR) and its 95% confidence interval (CI).

RESULTS

Study selection and characteristics

We identified 5,646 studies from our search. We exclude 5,592 studies after evaluation the title and abstract, that was excluded because intervention was not intravenous fluid resuscitation in a child with DSS; such as oral fluid resuscitation, steroid treatment and vaccine treatment. Fifty four studies were selected from the relevant studies, their full texts were retrieved and more detailed methodological evaluation was done. We excluded 51 studies due to 39 studies were not RCTs and 12 trials were duplicated. Only three studies were finally included in the analysis (Figure 1). The total number of patients reported in the three included studies were 784; 50 to 512 patients (Table 2). All three studies were conducted in Vietnam.

Risk of bias within studies

The three trials conducted in children with DSS in Vietnam were all double-blind randomized trials with adequate allocation concealment and adequate sequence generation. We used the Jadad score to assess the quality of selected articles; The first two studies received four scores and five scores in the last study, they all were high quality.

Study findings

Our main outcomes were the adverse events from using colloid and crystalloid including allergic reaction after infusion, new bleeding after studies and required diuretic (furosemide). Allergic reaction after infusion of crystalloids was lower compared with that of colloids (0% vs 4.4%; RR 0.08, 95 % CI, 0.01 to 0.62; P=0.02; I^2=0%). However, no significance differences regarding incidence of bleeding and requirement of diuretics were observed; the RR of new bleeding was 0.89 (95% CI, 0.57 to 1.40; P=0.62; I^2=0%); 8.4% in children receiving crystalloids and 13.5% in children receiving colloids. The rate of requiring for diuretic was similar between the two interventions (18.8% vs 26.1%; RR, 0.90; 95% CI, 0.45 to 1.78; P=0.76 I^2=73%. In one subgroup analysis with 2 RCTs of new bleeding comparing between lactated Ringer's solution and dextran, the rates of new bleeding were also similar between the two interventions (10.9% vs 13.3%; RR, 0.92; 95% CI, 0.55 to 1.52; P=0.74; I^2=0%).

In term of mortality outcome, none of the studies were designed or adequately powered to examine mortality. Only one trial with 512 children had reported only one death of profound shock and gastrointestinal bleeding after receiving starch. Because of the expected low mortality in DSS, this was not a stated end point. Therefore, no conclusion regarding the survival benefit between colloids and crystalloids can be drawn.

Outcomes from single study

In the study in 2001, we found no significant difference between the two interventions in relation to the pulse pressure recovery time (PPRT) more than 1 hour (P=0.05), re-shock rate (P=0.88). Another study in 2005, the rates using rescue colloid for

initial resuscitation were also no significant difference between the two interventions (P=0.78).

DISCUSSION

To our knowledge, this is one of the first systematic review that investigated the adverse event comparing between the use of colloid and crystalloid solution in children with DSS. In the present review, we found that allergic reaction were more common in patients receiving colloid than that of crystalloid solution. However, other outcomes regarding new bleeding and requirement of diuretics were similar between the two interventions. Death was found only one that received starch in the total of 784 children.

This is the review with the sample up to nearly 800 with very high homogeneity of the findings. All of the three included studies had high quality based on Jadad score assessment. However, there were some limitations in our study; firstly, the included studies were exclusively from Vietnam, this posed the problem of generalization of the findings to other settings. Secondly, the partly outcomes were come from only one study including to pulse pressure recovery time (PPRT) more than one hour, re-shock rate of patients and the rescue colloid for initial resuscitation. Thirdly, we were unable to systematically meta-analyze the clinical outcomes that evaluated in children with DSS such as pulse pressure, pulse rate, hematocrit and respiratory rate because of non-similar methods of outcome evaluation; two studies used mean with standard deviation and only one study used median with interquartile range. The reviewers had contacted to the authors of each study requesting for data, none of them responded.

Our results were supported by the findings of a previous systematic review that studied fluids for resuscitation in children with severe infection and shock which one episode of allergic reaction was reported in a child with severe malaria receiving gelofusine, a colloid solution.[10] DSS was prevalent in only some parts of the world, rate of many clinical outcomes such as death were low even in those with high severity, thus, large RCT might not be possible. Therefore, there were very few studies in especially RCT in dengue hemorrhagic fever.

In conclusion, only allergic reaction was more common in those with colloid solution. There were no differences in term of new bleeding and requirement of diuretics for children with DSS receiving either colloid or crystalloid solution. In addition to our outcomes from one study, it found that PPRT more than one hour, re-shock rate of patient and rescue colloid for initial resuscitation were also similar between using colloids and crystalloids. Thus, crystalloid solutions were more preferred for initial treatment in children with DSS. Longer and larger multi-national cohort should be conducted for better estimation of the effects of both benefit and harm of the two interventions.

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COMPETING INTERESTS: This study has no competing of interests.

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our motto

"I shall either find a way or make one"

-Hannibal Barca

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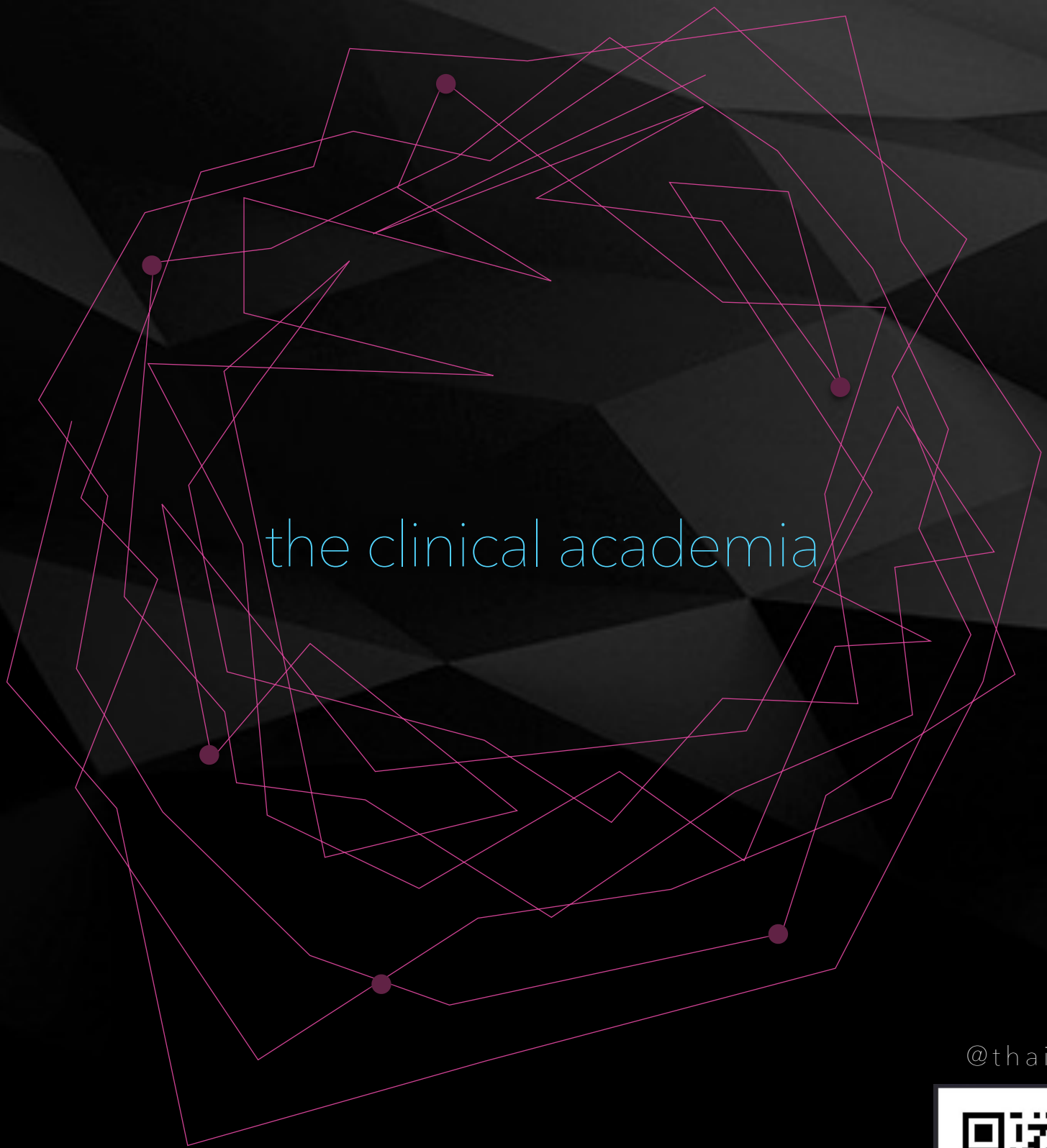
I don't want you to be only
a doctor but I also want you
to be a man
A quotation by His Royal Highness Prince Mahidol of Songkla



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