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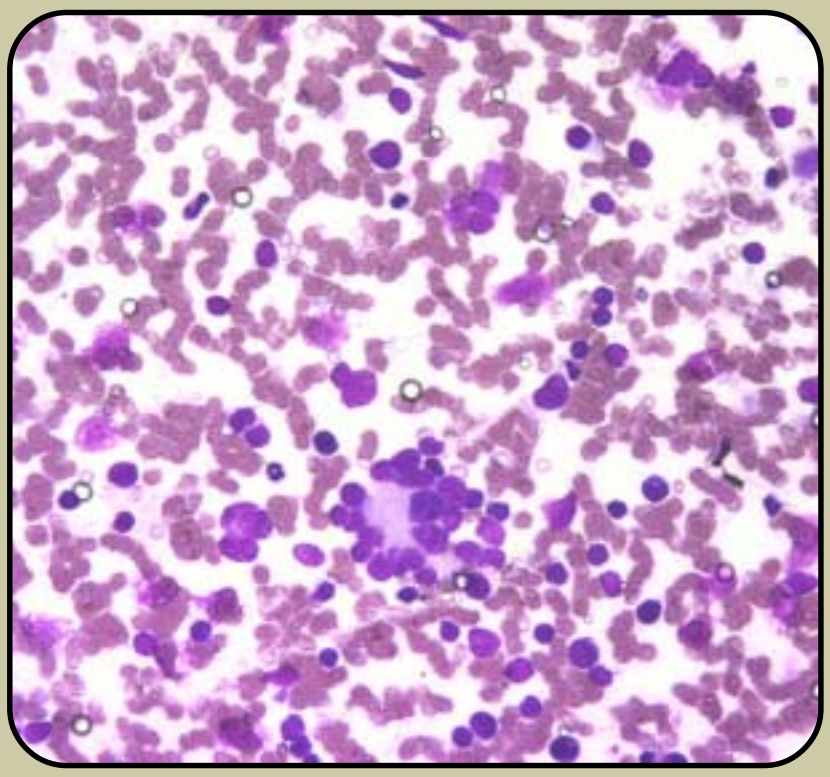

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Bone marrow infiltrated by neuroblastoma cells
(courtesy of Associate Professor Hany Mohd. Ariffin, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia)

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Manuscripts: Manuscripts must be in English not exceeding 3,000 words should be submitted in duplicate, typed on one side of A4 size paper and double-spaced with at least 2.5 cm margin. A computer diskette (3.5 in) or compact disc (CD) containing the manuscript in Microsoft Word and a covering letter, stating that the work has not been published or under consideration for publication elsewhere, should be submitted to the Editor. Presentations at meetings do not class as prior publication. The text of the manuscript should be in the following form:

Title page: The title page should contain a concise title of the article. It should identify all the authors, the name(s) of the institution(s) and their full addresses where the work was carried out. Contact information of the corresponding author including name, address, telephone, fax number and e-mail should also be indicated.

Abstract and Keywords: The second page should contain an abstract of about 150-200 words. It should state the purpose of the study, a brief description of the procedures employed, main findings and principal conclusions. Three to ten keywords should also be listed below the Abstract.

Text: Wherever possible, the text should consist of an introduction, materials and method, results, discussion conclusion, references and acknowledgements.

References: Number references consecutively in the order in which they are first mentioned in the text. References in the text should be indicated by a figure within parenthesis ( ). The titles of journals in the list should be abbreviated according to the style used in the Index Medicus. Authors are responsible for the accuracy of all references. Examples of correct forms of references are given as follows:

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Roberts CW, Alexander J, Bossi L, *et al*. Studies on a murine model of congenital toxoplasmosis. Parasitol 1992; 104:19-23.

ii) Personal author(s) of book:
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iii) Chapter in book:
Weinstein L, Swartz MM. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders; 1974; 457-72.

iv) Agency publication:
World Bank. Intensifying Action Against HIV/AIDS in Africa: Responding to a Development Crisis. 2000, 89p.

v) Journal article on the Internet:
Foley KM, Gelband H, editors. Improving Palliative Care for Cancer. Washington National Heading Press; 2001 *www.nap.edu/books/0309074089/html*. (accessed 14 Apr 2006).

Abbreviations, Symbols and Nomenclature: A list of acceptable abbreviations is published in the Uniform Requirements for Manuscripts submitted to Biomedical Journals (also known as the Declaration of Vancouver). For more information, refer to:

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Only generic names of drugs may be used. Quantitative data must be reported in SI units.

Tables: Type each table on a separate sheet and number in arabic numerals. The tables should be as few and as simple as possible, with the title above and any notes or description below. Explain all abbreviations. If a table or figure has been published before, written permission must be given by the owner for its reproduction.

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Healthy Lifestyles

Healthy lifestyle issues have been very much in the news in both the lay press and the medical journals. The incidence of chronic non-communicable diseases is increasing worldwide and it is no different in Malaysia. Preventing and decreasing the incidence is related to lifestyle issues.

Before we start to deal with these issues, we need to know the extent of the problem in our community. These problems are addressed by two articles in this issue of JUMMEC.

Obesity is a problem which has been noted to be an epidemic in the west and is beginning to creep into our society. Sharif AH *et al* (1) discuss the problem of obesity among urban primary schoolchildren. They have noted the overall incidence of obesity at 9.5% based on BMI but a lower level of 3.0% based on the definition of International Obesity Task Force. These figures are lower than the earlier study done by Anuar Zaini *et al* (2), who studied a larger population. They also showed that the problem of obesity is similar among the three major ethnic groups in the country.

Physical activity is very much related to the problem of obesity. Ayiesah R (3) studied the level of physical activity among the elderly. The elderly patients were defined as those above 60 years. The group was identified from those attending the KL Health Clinic. The patients were asked to answer a self-administered questionnaire. Overall 57.1% of them were noted to be physically active, in activities that included walking, gardening, cycling, tai chi and stretching. However the levels of these activities were not mentioned. The Chinese were most active followed by the Indians and the Malays. The reason for the difference is not clear and can be a topic to be looked into in the future.

National athletes such as the Malaysian netball players are among the most physically active members of the society and are involved in various training programmes on agility and leg power. After eight weeks of training there was no significant improvement in the agility and leg power of these players overall. However, a marginal improvement on both these parameters was noted for the attacker and centre players, but not for the defender. The authors did not suggest reasons for their findings.

Breastfeeding is also a lifestyle and population education issue, and it is very important for the medical community to play a role in enhancing this practice. The University of Malaya Medical Centre, Kuala Lumpur was recently given the recognition of Baby Friendly Hospital by the Ministry of Health, Malaysia. To this end, health care workers must be trained with the necessary skills and knowledge to stop the decline in breastfeeding. Tan KL and Ghani SN (4) did the first local study to assess the effectiveness of the lactation management course organised by the local district health office. The effectiveness was assessed by the pre- and post-training test scores. The participants showed significant improvement in scores after the course. It is interesting to note that the four doctors, who participated, did not show significant improvement.

In the era of evidence-based medicine (EBM), systemic review and meta-analysis has become important in assessing the evidence available in published literature. To be able to benefit from the review and analysis, it is important that the terms are clearly understood. Wong LP (5) has written a very clear and concise article on the definition of the commonly used terms. It is a very useful article for all, especially those doing literature search prior to embarking on a particular research.

The only case report in this issue is an interesting case of agranulocytosis secondary to carbimazole treatment of thyrotoxicosis in a pregnant woman. The article discusses in detail the management of this rare condition.

Evidence that JUMMEC continues to grow in strength and quality is provided by the article from the Department of Paediatrics. Daud SS, Ibrahim K and Arriffin H (6) report on the monitoring of haematopoietic stem cell transplant patients with high resolution microchip electrophoresis to predict relapse in these patients. Their method of chimerism analysis can help identify early relapse so that commencement of therapeutic intervention is not delayed. This, in turn, can lead to improved long-term outcome. However, this method needs validation with a larger number of cases.

With the quality of articles improving with each issue, JUMMEC will continue the quest to become an important medical journal at the national and regional level. This can in turn encourage more academic staff and researchers to submit their work to JUMMEC.

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SYSTEMATIC REVIEW AND META-ANALYSIS: A GLOSSARY

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ABSTRACT: Systematic review is a comprehensive review of research findings in which all of the primary studies are systematically identified, appraised and summarised using an explicit and reproducible methodology. Meta-analysis is the statistical component of a systematic review in which combinable studies are drawn together via a statistical process. Systematic reviews and meta-analyses are routinely being used in the evidence-based approach to medicine. These short notes intend to highlight important terms in systematic-review and meta-analysis. It is a beginner's guide for health care professional of any discipline involved in research or practice who seeks to gain more comprehensive understanding of important terms used in systematic review and meta-analysis. *(JUMMEC 2007; 10(1): 3-10)*

KEYWORDS: Systematic review, meta-analysis, glossary

Introduction

Important medical questions are often studied more than once by different research teams in different locations. Systematic reviews are a type of secondary research that evaluate the results of previous research, usually randomised trials that have addressed the same clinical question. A systematic review is a comprehensive survey of a topic in which all of the primary studies are systematically identified, appraised and then summarised according to an explicit and reproducible methodology. The review aims to review clearly formulated questions, using explicit methodology to minimise bias in the location, selection, critical evaluation and synthesis of research evidence. It is an objective way of assembling, assessing and summarising evidence to give a full and fair evaluation of the treatment under investigation and to provide a structured basis for evidence-based medicine. Where possible, the results of individual studies are combined in a meta-analysis. Systematic review of the literature can be applied to any form of research question. Often, a systematic review will include a meta-analysis.

Meta-analysis is a quantitative method of combining the results of research studies to provide overall summary statistics. Often, many trials lack power (i.e. adequate sample size) to achieve statistically significant results. Combining the results of similar trials in a meta-analysis may give sufficient statistical power to reach a clear and more reliable answer. A good quality meta-analysis should always be done in the context of a systematic review. These glossaries highlight important terms in systematic review and meta-analysis as a beginner's guide for researchers of any discipline.

Allocation concealment: Process used in studies that involve at least two groups receiving different interventions or treatments where allocation to treatment is done in such a way that the participants and health care providers do not know which intervention the participant is to receive. Allocation concealment aims to avoid bias during the group allocation process so that the intervention and control groups are similar. Assessment of methodological quality in systematic reviews should consider whether allocation was adequately concealed. Normally, studies would be excluded from inclusion if no allocation concealment was used or if there was uncertainty about the allocation concealment.

Apples and oranges: When examining the results of a meta-analysis, the question often asked is: Were apples combined with oranges? If the pooled studies are too dissimilar, the meta-analysis may be combining apples and oranges, rather than different types of oranges. The problem of heterogeneity arises, resulting from the

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basic differences that exist between trials. This includes differences such as in the quality of their designs, the eligibility criteria for inclusion or the treatments used. If the trials are too dissimilar, combining trials may increase the statistical precision of the result, but it decreases its clinical reliability. Trials should be combined only if they are sufficiently alike.

Bias: Distortion of the outcome is due to known or unknown differences between groups other than intervention. Bias in meta-analysis arises mainly from a) choice of studies included in the meta-analysis and b) how the results of selected studies are combined to produce an overall effect estimate. Selection bias refers to bias in how studies are selected for inclusion. Publication bias is inclusion of only published studies. This is because studies which do not show the intervention to be effective are often not published. Systematic reviews that fail to include unpublished studies may result in an overestimate of the true effect of an intervention. Attrition bias is systematic differences between comparison groups in withdrawals or exclusions of participants from the the study. Detection bias refers to differences in the assessment of outcomes. Performance bias refers to systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation.

Cochrane Collaboration: An international organisation that aims to make up-to-date information about the effects of healthcare available so that people can make well-informed healthcare decisions. The Cochrane Collaboration (http://www.cochrane.org) produces and disseminates systematic reviews of healthcare interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. The Collaboration encompasses an established network of 50 research groups worldwide that prepare and maintain Cochrane reviews, covering a range of medical specialties.

Confidence interval (CI): The CI combines information on the sample size and variance to put probabilistic bounds on estimates of an effect. In a Forest plot of log odds ratios and confidence intervals, the vertical line on the plot corresponds to an odds ratio of one, where treatment and control are equally effective (*see* Forest Plot). CI which includes this value implies no statistically significant effect was found. In other words, any interval not including one indicates significant effect.

Critical appraisal: Systematically finding, appraising and interpreting evidence of effectiveness. It is aimed to examine research to assess its validity, results and relevance before using it to form a decision.

Cumulative meta-analysis: The repeated performance of meta-analysis whenever a new trial becomes available for inclusion. In cumulative meta-analysis, studies are added one at a time in a specified order (e.g. according to date of publication or quality) and the results are summarised as each new study is added. In a graph of a cumulative meta-analysis, each horizontal line represents the cumulative summary of the results, rather than the results of a single study. In a cumulative meta-analysis plot, each study added increases the sample size and this should result in progressive narrowing of the confidence interval demonstrating, a change in point of estimate and shows how evidence has accumulated over time.

DerSimonian-Laird's method: Random effects model used in meta-analysis. It is based on the risk difference and weighted by the inverse of its variance (*see* random effects model).

Effect size: Refers to the size of a relationship between an exposure and an outcome. The term is applied to the measurement of the difference in the outcome between the study groups. Relative risk, odds ratio, and risk differences are measures of effect size. The effect size of a continuous variable is expressed as the standardised mean difference. Effect size can be measured in two ways: a) as a standardised difference between two means, or b) as a correlation between the independent variable classification and the individual scores on the dependent variable. This correlation is called the "effect size correlation".

Egger's plot: Used to investigate the possibility of a publication bias. It is a simple linear regression of the effect size in a study divided by its standard error on the inverse of standard error testing whether the intercept is statistically significant. The 95% confidence intervals of the regression line's *y* intercept should include zero if there is no evidence of publication bias (Figure 1).

Evidence-based medicine: A new approach to teaching the practice of medicine. It is a conscientious, explicit and judicious use of current best evidence in making decisions about certain aspects of medical practice. The practice of evidence-based medicine requires careful balancing and integration of three key components, namely, the best available evidence, clinical expertise and patient values. The goal of evidence-based medicine is to improve health care quality and patient outcomes across the health care system.

Fixed effect method: There are four widely used methods for estimating a combined effect estimate in meta-analysis for dichotomous outcomes, three fixed

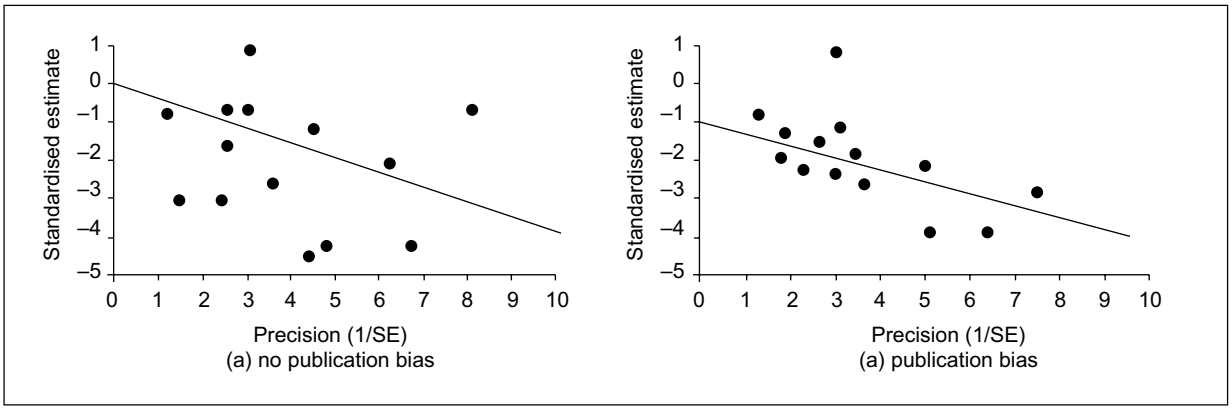

Figure 1. Regression line of estimate against precision (1/standard error)

effect methods (Mantel-Haenszel, Peto and Inverse Variance) and one random effects method (DerSimonian and Laird). The fixed effect method considers only within-study variability. Variation between the estimates of effect from each study does not affect the CI in a fixed effect model. The assumption is that studies use identical methods, patients, and measurements; that they should produce identical results; and that differences are only due to within-study variation (*see* random effect method).

Forest plot: Schematic display of the results of a meta-analysis where point estimates and 95% CIs for each study, along with the overall summary estimate and CI represented as a diamond at the bottom.The weight of each study is represented by the size of the box, indicating the estimated treatment effect. Significance is achieved if the diamond is clear of the line of no effect (Figure 2).

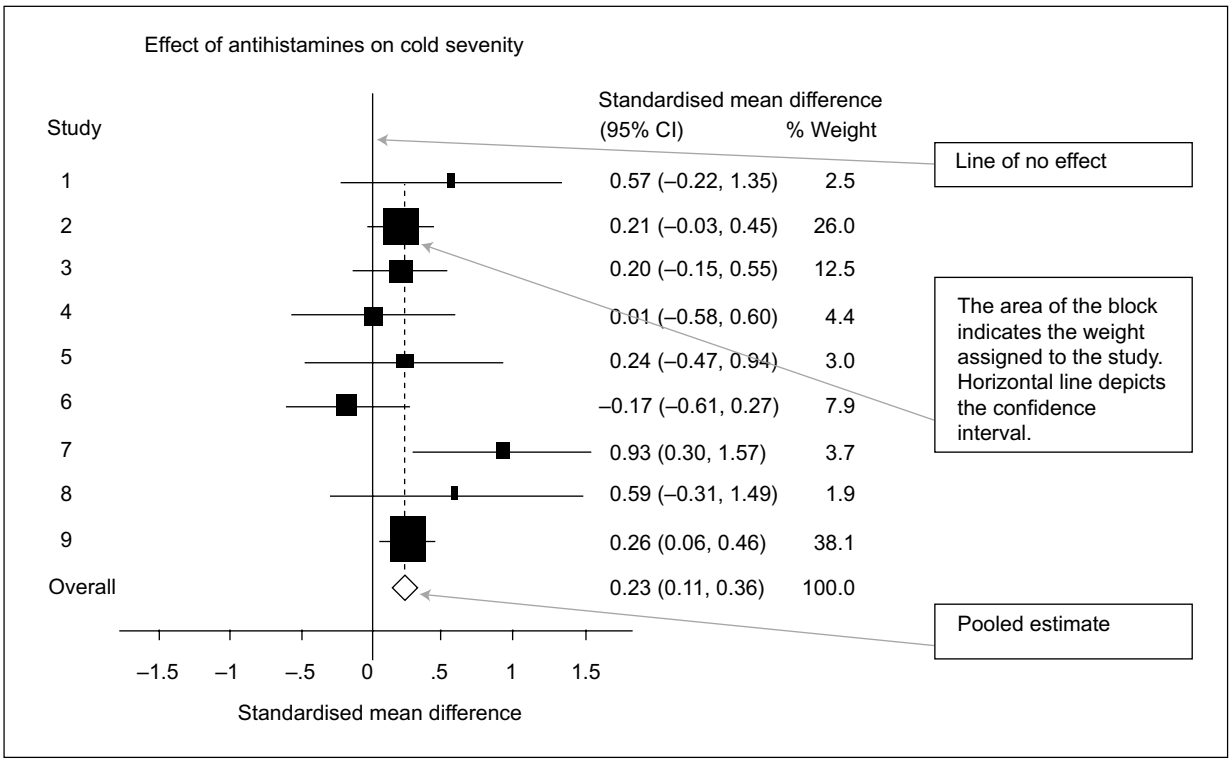

Figure 2. Forest plot meta-analysis of the effect of antihistamines on cold severity

Funnel plot: A graphical display of a plot of effect size against sample size or other indicator of precision of estimate. It is a visual tool to investigate publication bias. Funnel plots should have variance or precision (often sample size is used as a measure) on the *y*-axis. A plot should shape like an inverted funnel if there is no publication bias. Asymmetrical plots are interpreted to suggest that bias is present (Figure 3). Visual inspection of funnel plot may not be a reliable method of investigating publication bias. Egger's linear regression test and Begg's rank correlation test are two types of statistical test for the asymmetry of funnel plot.

Garbage in, garbage out: A common criticism of meta-analysis refers to meta-analyses of studies where the primary studies and the selection of studies for inclusion are poorly conducted. The major concern is the quality of the primary research included in systematic review. If invalid studies are pooled, the resulting overall estimate will also be invalid. Therefore, studies with methodological flaws should not be included in the meta-analysis.

Heterogeneity: The variation between the pooled studies. Heterogeneity in meta-analyses creates difficulty in drawing overall conclusions. There will usually be variations in patient groups, clinical settings, concomitant care and method of delivery of intervention as the trials are not conducted according to a common protocol. Variability between the results of studies can be examined by a test of homogeneity (see test of homogeneity). Common methods for investigating and dealing with sources of heterogeneity are sensitivity analysis, subgroup analysis, meta-regression, and cumulative meta-analysis.

Homogeneity: Homogeneity measures the differences or similarities between the several studies. If several studies reach nearly the same conclusion, one can combine the data with reasonable confidence. If the studies differ greatly in their outcomes, one should be more cautious about combining the data. Test of homogeneity may be used to assess homogeneity. To reach homogeneity, the authors remove the most extreme effect sizes, irrespective of whether they were extremely high or extremely low, until homogeneity is reached – if possible. Otherwise, the studies cannot be compared with one another with confidence.

Inverse of variance: The inverse variance method of performing a meta-analysis is so named because the weight given to each study is chosen to be the inverse of the variance of the effect estimate (i.e. one over the square of its standard error). Thus larger studies, which have smaller standard errors, are given more weight than smaller studies, which have larger standard errors. The choice of this weight minimises the imprecision (uncertainty) of the pooled effect estimate.

L'Abbé plot: Usually used for meta-analysis of randomised controlled trials (RCTs) where the outcome is a binary variable. The L'Abbé plot shows the proportion with the outcome in each group (e.g. outcome in the treatment group versus outcome in the control; outcome in the exposed group versus outcome in the unexposed group). If the trials are fairly

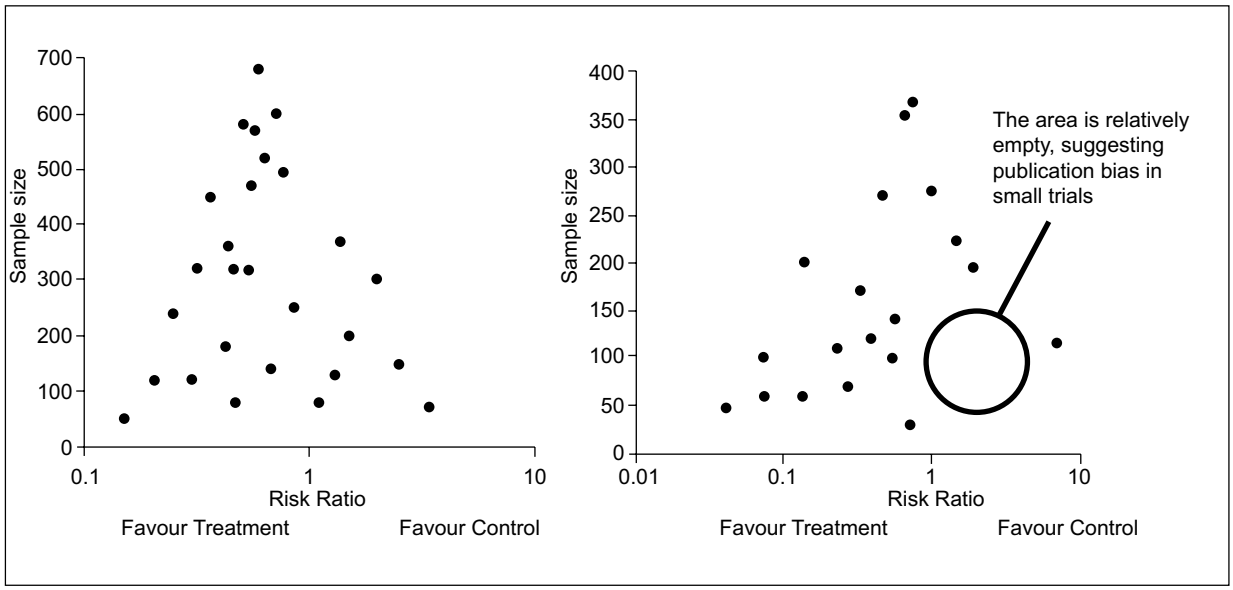

Figure 3. Funnel plot showing evidence of publication bias

homogeneous, the points should form a cloud close to a line, the gradient of which would correspond to the pooled treatment effect. Large deviations or scatter indicate possible heterogeneity (Figure 4).

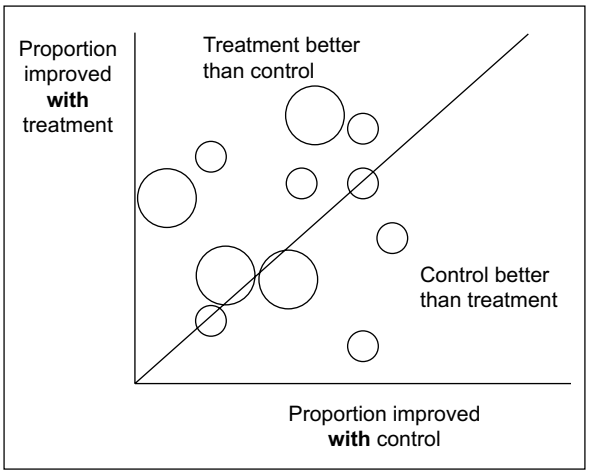

Figure 4. L'Abbé plot shows the proportion with the outcome in each group versus outcome in the control

Limitations of meta-analysis: Authors of the meta-analysis must assess the limitations of their analysis and decide what conclusions to state. Meta-analysis can be subject to data limitations and if the included studies have bias or flaws, the meta-analysis will also be flawed. Secondly, if there is a lack of consistency across studies in the composition of study population, study design or outcome measures, it will be difficult to generalise the results.

Log-odds ratio: The log of the odds ratio, used in statistical calculations in the graphical displays of odds ratios in systematic review.

Mantel-Haenszel's method: A statistical method (fixed effect) for pooling individual studies (relative risk, odds ratio and rate ratio). Mantel-Haenszel method is a method of stratified analysis of data. In Mantel-Haenszel's method, each study is considered a strata.

Meta-analysis: A method of combining independent studies that have investigated the same question and used similar study methods to produce a single estimate (Figure 5). It is often used as part of a systematic review but can be performed on studies that are not part of a systematic review. The main aim of a meta-analysis is to produce an estimate of the average effect, and the direction and magnitude of the average effect is intended as a guide in making decisions about clinical practice. The estimate of an average effect is calculated as weighted average, defined as:

$$\text{Weighted average} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}} = \frac{\sum T_i W_i}{\sum W_i}$$

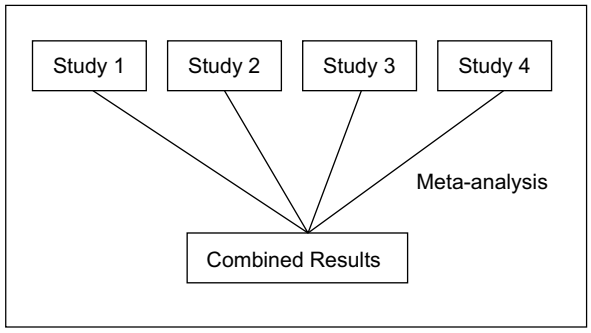

Figure 5. Combination of data from independent studies to produce a single estimate

where T_i is the treatment effect estimated in study *i*, W_i is the weight given to study *i*.

Meta-analysis of Individual Patient Data (IPD): Obtaining information or raw data on all patients included in each of the trials directly from those responsible for the trial. Collecting individual patient data (IPD) has been described as the 'gold standard' for undertaking meta-analysis. This method relies heavily on the international cooperation between the individuals and groups who have conducted relevant trials. IPD may be very time consuming and resource intensive, nevertheless, it has several advantages such as possibility of checking data consistency, provide update follow-up data, and ensure the appropriateness of the analyses.

Meta-regression: Meta-regression is an extension to meta-analysis, and a generalisation of subgroup analyses, that can be used to investigate heterogeneity of effects across studies. It examines the relationship between one or more study-level characteristics and the sizes of effect observed in the studies. Meta-regression can formally test whether there is evidence of different effects in different subgroups of trials. Figure 6 shows a weighted regression line between treatment effect and

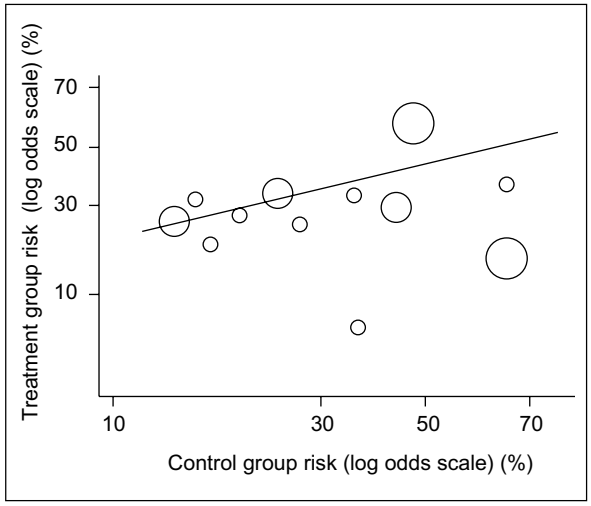

Figure 6. Meta-regression of treatment effect and underlying risk

underlying risk. Circles indicating the studies and size of circle show the weight of each study.

Narrative review: A "traditional" or "narrative" review (also known as overviews) may be no more than a subjective assessment by an expert using a select group of materials to support their conclusion and are therefore prone to bias and error. The procedure ignores search strategy, sample size, effect size and research design. The common way to review the results is to count the number of studies supporting various sides of an issue and to choose the view receiving the most votes.

Outlier: An outlier study in meta-analysis is a study that has results very different from the rest of the studies. An outlier could alter the conclusions of a meta-analysis. If a study appears to be an outlier and the inclusion of its data into the meta-analysis resulted in heterogeneity, it should be excluded from the meta-analysis.

Peto's method: Peto's method of performing meta-analysis is similar to Mantel Haenszel's but computationally simpler. It can be regarded as a modification of the Mantel Haenszel's method.

Pooled estimate: Pooled estimate is the weighted average of each individual sample's variance estimate. In a Forest plot the centre of the diamond represents the pooled point estimate (*see* Figure 2).

Publication bias: The phenomenon by which significant and positive results are more likely to be reported, and reported more prominently, than non-significant and negative results. A simple analysis of funnel plots provides a useful test for the likely presence of bias in meta-analyses. Funnel plots, plots of the trials' effect estimates against a measure of precision such as sample size, are skewed and asymmetrical in the presence of publication bias and other biases. Statistical tests for publication bias are Begg's test and Egger's test.

Qualitative meta-analysis: To appraise the quality of qualitative research results for inclusion in systematic review. Meta-synthesis of qualitative research basically follows the same, replicable procedure of a quantitative meta-analysis. However, unlike quantitative research synthesis, a qualitative meta-analysis is interpretative rather than aggregative. It involves analysis of the theories, methods and findings of qualitative research and the synthesis of these insights into new ways of thinking about a phenomenon. Instead of a statistical data analysis, the researcher analyses textual reports, creating new interpretations in the analysis process.

Random effects model: Considers both between-study and within-study variability. The assumption is that individual studies are a random sample from the universe of all possible studies. The DerSimonian Laird statistic is based on a random effects model. Random effects models are more *conservative* and generate wider confidence intervals. A random effects model is less likely to show a significant treatment effect than a fixed effects model and give wider CIs than fixed effect models.

Retrieval of studies: Includes three important steps. First, reviewer decides on the comprehensiveness of the search. Once potentially useful studies are identified, they must be obtained. Finally, the reviewer must determine which studies to include in the review. Search strategies and inclusion criteria must be clearly defined.

Search strategy: Description of the methodology to be used to locate and identify research articles pertinent to a systematic review. It includes a list of search terms, based on the subject, intervention and outcome of the review to be used when searching electronic databases, websites, reference lists and when engaging with personal contacts.

Selection bias: The introduction of error due to systematic differences in the characteristics of those selected to participate in a study, or receive an intervention. Selection bias is also used to describe a systematic error in reviews due to how studies are selected for inclusion.

Sensitivity analysis: Repetition of the analysis using different sets of assumptions to determine the impact of variation arising from these assumptions. Sensitivity analysis may examine the consistency of results across various subgroups (e.g. patient group, type of intervention or setting). Sensitivity analysis was undertaken using subgroup analysis.

Subgroup analysis: Subgroup analyses are meta-analyses on subgroups of the studies aimed to determine if the effects of an intervention vary between subgroups. Subgroups may be predefined according to many factors including: differences in subject populations, intervention, and outcome and study design.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Systematic reviews are often carried out to find all the results of all the studies on a particular topic, and then the

Table 1. Systematic review versus narrative review

Characteristic	Systematic Review	Narrative Review
Search strategy	Comprehensive search of many database as well as gray literature. Uses explicit search strategy	No explicit methods for searching or reporting results
Selection criteria	Criterion-based selection, uniformly applied	Usually not specified, potentially biased
Article review or appraisal	Rigorous critical appraisal, typically using a data extraction form	Variable, depending on who is conducting the review
Assessment of study quality	Assessment of quality is always included as part of the data extraction process	May not use formal quality assessment
Synthesis	Quantitative summary (meta-analysis) if the data can be apropriately pooled; qualitative otherwise	Often a qualitative summary
Replicate	Can be replicated	Cannot be replicated

results may be combined together using meta-analysis to produce one overall result. A systematic review may, or may not, include a meta-analysis, however, a quantitative systematic review is synonymous with meta-analysis.

In contrast, a traditional or narrative review may be no more than a subjective assessment by an expert using a select group of materials to support their conclusion (Table 1).

Test of homogeneity: A statistical test to assess whether individual study results are likely to reflect a single underlying effect, as opposed to a distribution of effects (also called tests of heterogeneity). If a test of homogeneity fails to detect heterogeneity among results, it is assumed that the differences observed between individual studies are a consequence of sampling variation and simply due to chance. A major limitation of the statistical tests of homogeneity that are in use is the lack of power. Therefore, a non-significant test of heterogeneity does not necessarily exclude heterogeneity. Cochran's Q test is the standard test for testing homogeneity in meta-analysis.

Trial validity: The degree to which a result is likely to be true and free of bias. Assessment of each trial's validity is critical in systematic review. An important dimension of study quality relates to the validity of the findings generated by the study. There are two important forms of validity: internal and external validity. Internal validity is defined as the extent to which the results of a trial are valid for the conditions being studied. External validity is the extent to which results of a trial provide a correct basis for generalisations.

Weighted mean difference: A method of meta-analysis used to summarise effect size measures for continuous data where the weight given to each study is determined by the precision of its estimate and effect. The weight given to each study is determined by the precision of its estimate of effect and is equal to the inverse of the variance.

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QUANTITATIVE EVALUATION OF CHIMERISM STATUS FOLLOWING HAEMATOPOEITIC STEM CELL TRANSPLANTATION USING A MICROCHIP ELECTROPHORESIS SYSTEM

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ABSTRACT: We aimed to establish a method for quantitative analysis of mixed haematopoietic chimerism based on microchip electrophoresis of selected molecular markers following PCR amplification for accurate monitoring of graft status post-transplantation. A 12-year-old girl with relapsed acute lymphoblastic leukaemia who underwent allogeneic bone marrow transplantation had qualitative chimerism analysis using short tandem repeat markers at three time points following the procedure. Her archived DNA samples were then used to test the ability to correlate her clinical course with changes in the quantity of donor chimerism at the different time points. Quantitative chimerism analysis was performed on the Agilent 2100 bioanalyser and donor-recipient ratios were calculated from generated electropherograms. Complete donor chimerism (98%) was demonstrated three weeks post- transplantation. Decreasing amount of donor chimerism to 24% was shown after three months and this concurred with clinical relapse. Following a second transplant, full donor chimerism was re-established where donor chimerism rose to 100%. High resolution microchip electrophoresis could be useful in predicting the occurrence of increasing recipient chimerism which may herald impending relapse in patients while the disease burden is still low. This investigational approach may provide useful information for clinicians to select appropriate intervention strategies to ensure successful transplantation. *(JUMMEC 2007; 10(1): 11-16)*

KEYWORDS: Haemopoeitic stem cell transplantation (HSCT), chimerism analysis, Short Tandem Repeats (STR)

Introduction

Haemopoeitic stem cell transplantation (HSCT) has been used in the treatment of many malignant and non-malignant disorders in children since the 1970s. The paediatric HSCT unit of the University of Malaya Medical Centre (UMMC) was established in 1987 and has performed more than 300 transplants from both sibling and unrelated cord blood donors.

Following transplantation, it is of great importance to determine whether engraftment has occurred successfully. The investigation of the genotypic origin of post-transplant haematopoeisis is called chimerism analysis. Since chimerism analyses were first performed, many different methods have been developed. The basic principle in these studies has been demonstrating differences (or similarities) of genetic markers between the donor and recipient (1). Early methods included red cell phenotyping (2) and determination of sex chromosomes by either conventional karyotyping or fluorescence in situ hybridization (FISH) (3). However, these methods are not feasible in patient-donor pairs who share red cell antigen types or those who are of the same gender.

In the 1990s, detection of molecular markers, namely, variable number of tandem repeats (VNTR) or short tandem repeats (STR) was developed for chimerism studies (4,5). The paediatric oncology research laboratory of the UMMC commenced chimerism

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studies using PCR amplification of STR markers in April 2005. To date, engraftment information has been provided for over 30 adult and paediatric patients. However, clinical decisions for the management of mixed chimerism state have been hampered by the lack of quantitative data and the inability to monitor trends in donor-recipient ratios.

To overcome this problem, we developed a method to accurately quantify donor chimerism where this information can aid clinical decisions with regards to manipulating a graft, for example using donor lymphocyte infusion. Here, we demonstrate the use of microchip electrophoresis for quantitative chimerism analysis and correlate it with a patient's clinical course.

Patient and Methods

Case Report

MW is a 12-year-old girl with relapsed acute lymphoblastic leukaemia, who underwent allogeneic bone marrow transplantation at the Subang Jaya Medical Centre (SJMC), Selangor in November 2005. Her elder sister was her donor. Marrow samples were obtained at three time points (TP1, TP2 and TP3) which were at week 3 and at the third and fourth months, respectively, after her transplantation. Amplification of short tandem repeats (STR) DNA followed by PAGE electrophoresis were used to assess donor chimerism.

Two STR markers (CSF1P0 and TH01) were found to be informative and able to provide information on engraftment status. Full engraftment was shown at week 3 post-transplant (TP1) depicted by sole presence of donor bands (Figure 1).

At three months of post-BMT (TP2), she was noted to have a rapid rise in the total white cell count. Chimerism studies done at this point in time showed the presence of a hitherto undetectable recipient band (Figure 2). Subsequent bone marrow examination revealed frank relapse of leukaemia. Since no sample was sent for STR monitoring between TP1 and TP2, we were not able to show the point where early prediction of relapse was possible.

Following chemotherapy, she underwent a second transplantation from the same donor in March 2006. Analysis done one month after the second transplantation (TP3) showed that she had changed to full donor chimerism. This was concordant with the presence of complete remission status by bone marrow morphology and by minimal residual disease analysis performed in Singapore. At the time of writing (8 months following the second BMT), she remains in continued clinical remission.

Genomic DNA extraction

Peripheral blood samples were obtained prior to BMT from MW and her donor and subsequently at three time points as stated above. DNA was extracted using the modified phenol chloroform method and ethanol precipitation (6). The extracted DNA was suspended in sterile nuclease free double distilled water and kept at 4°C.

Purity of DNA samples were checked and quantified prior to subsequent testing using an automated spectrophotometer (Eppendorf AG, Germany). Purity and concentration were estimated from the optical density ratio (OD260/OD280) with a range of purity between 1.7 and 1.9.

Multiplex STR Polymerase Chain Reaction

Multiplex STR amplification was performed using GenePrint™ CTT Multiplex System (Promega, Madison, WI, USA). Each kit simultaneously amplifies three autosomal tetranucleotide STR loci with non-overlapping allele size ranges. Loci in the CTT kit are CSF1PO, TPOX and TH01. PCR amplification was performed using 100 ng template DNA on a GeneAmp PCR System 9700 thermocycler (Applied Biosystems, Foster City, CA, USA). PCR was carried out in a final volume of 25 µl using 10X STR buffer, 10X multiplex primer pair mix (Promega) and 0.75 U of HotStar Taq™ DNA polymerase (Qiagen, Hilden, Germany). Ten nanograms of K562 DNA served as positive amplification control to validate the result.

Initial PCR consisted of activation of the polymerase at 96°C for 2 minutes, followed by the first 10 cycles of PCR amplification (denaturation at 94°C for 1 minute, annealing at 64°C for 1 minute and elongation at 70°C for 1.5 minutes). It was then followed by different PCR parameters for another 20 cycles where denaturation occurred at 90°C for 1 minute, annealing for 1 minute and elongation at 70°C for 1.5 minutes.

Quantitative PCR analysis

Archived PCR products taken at the three time points above were used in this study. Quantification of PCR products were accomplished using an Agilent 2100 bioanalyzer (Agilent Technologies, Palo Alto, USA) in conjunction with the DNA 1000 Labchip kit. The chip contains 16 wells: 3 for loading of the gel fluorescent dye mixture, 1 for the molecular size ladder, and 12 wells for samples. One microlitre of each PCR product was used for analysis. The migration and automated analysis were completed in 30 minutes. Results were

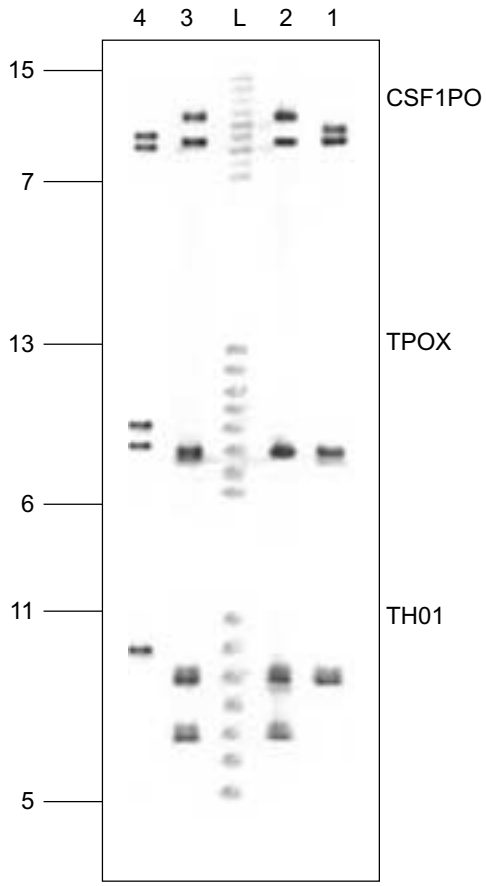


Figure 1. Full engraftment showed by STR PCR of CTT Multiplex System

Lane 1 : DNA from patient before transplant.
Lane 2 : DNA from donor.
Lane 3 : Donor specific alleles of two informative loci; CSF1PO and TH01 in week 3 post-transplantion sample.
Lane 4: K562 control DNA showing expected allele sized.
L : Allelic ladder showing number of repeat units form the respective STR loci.

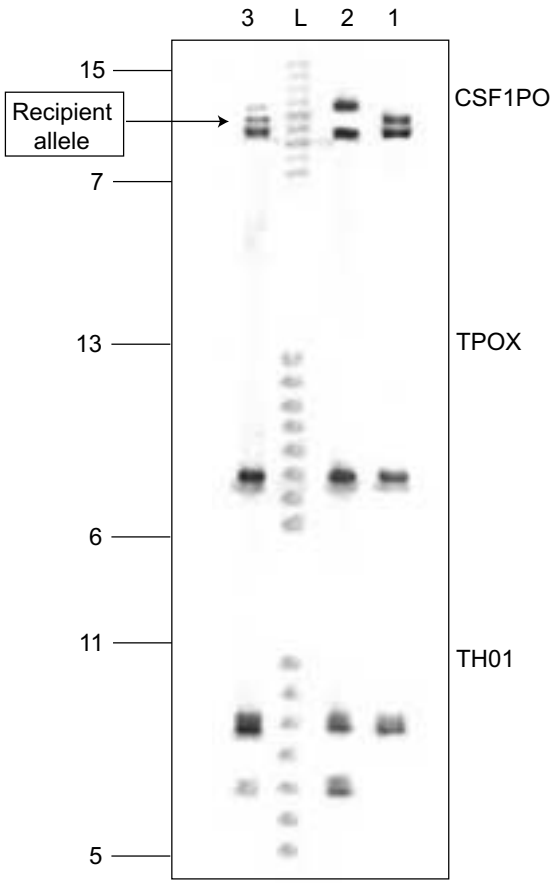


Figure 2. Mixed chimerism of donor and patient DNA, detected with STR PCR of CTT Multiplex System

Lane 1 : DNA from patient before transplant.
Lane 2 : DNA from donor.
Lane 3 : Donor specific allele 11 of CSF1PO locus was present together with donor specific allele; 3 months post-transplantation. There was a decrease in the relative intensity of the donor specific bands.
L : Allelic ladder.

shown in three formats: gel-like image, electropherograms and data table. The bioanalyzer software package was used to correlate allele peak areas to the percentage of donor or recipient DNA.

Results

Results of the quantitative chimerism studies are summarised in Figure 3. A sudden rise in the patient's peripheral white cell count, associated with disease relapse, was shown by decreasing amounts of donor chimerism to 24%. Following a second bmt (TP3), full donor chimerism was re-established where donor chimerism rose to 100%.

Discussion

One rationale for monitoring chimerism following allogeneic transplantation is that it may enable prompt therapeutic intervention to treat early relapse or rejection; leading to improved outcome. Also, analysis of chimerism may be of value as an alternative to monitoring minimal residual disease. The significance of mixed chimerism will depend on the time at which it is detected and the pattern of change in the proportion of recipient cells.

Quantification depends on identifying and measuring genetic markers that differ between the donor and the graft recipient. Full engraftment or complete chimerism refers to complete replacement of host cells by donor haematopoiesis. Also, no evidence of recipient cells should be present at any time post-transplantation (7). Quantitatively, it is defined by the presence of <2% of recipient cells in bone marrow or peripheral blood (8). This is the ideal haematological status and the patient is usually associated to be free of disease.

Mixed haematopoietic chimerism can be defined as the detection of 2.5-97.5% cells of donor origin in haematopoietic tissues, which approximately defines the sensitivity of routinely used assays for quantifying chimerism (5,9). In malignant diseases, persistent mixed chimerism state may be caused either by regeneration of normal recipient haematopoeitic cells (10) or emergence of leukaemic cells. Barrios *et al* reported in 133 leukaemia patients, those with increasing mixed chimerism of more than 5% of recipient cells have a significantly higher risk (94%) of developing relapse and death compared to patients who showed low levels of persisting recipient cells (11). Similar findings have been reported by Bertheas (12). The time interval between the detection of mixed chimerism and the onset of relapse was reported to range between five to 434 days (11, 13).

It is clear that it is not a mixed chimerism state per se but an increasing amount of recipient cells (or decreasing donor chimerism) which is important for prediction of relapse. Thus, serial quantitative analysis showing increasing recipient chimerism may identify a cohort of patients with impending relapse which may be prevented by pre-emptive immunotherapy.

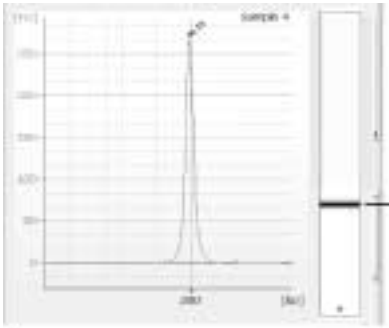
In the present study, analyses of recipient and donor DNA polymorphisms were carried out using the Agilent 2100 system that is capable of rapidly analysing small DNA fragments of up to 12 samples per run. A virtual gel image is also available together with electropherograms showing the fluorescent unit of each peak upon completion of electrophoresis.

In this series of follow-up samples, the donor and recipient alleles of TH01 were successfully separated since the base-pair size difference was more than 6 base pairs. The other informative STR locus CSF1PO was not analysed as the close base pair size difference of the recipient and donor alleles caused overlapping of the electropherograms. The DNA 1000 Labchip assay that we used is able to separate alleles with a size range of 25-1000 base pairs (14).

The time interval between HSCT and molecular analysis by STR or VNTR has been reported to affect the degree of mixed chimerism and prediction of relapse. The sensitivity of methods may be partly attributed to the degree of mixed chimerism detected. Mixed chimerism detection using STR has a sensitivity limit in the range of 0.5 to 2.5% to detect a band or peak for a minor cell population (7,15). Obviously, the usage of a more sensitive detection method will improve our ability to detect the occurrence of mixed chimerism in future.

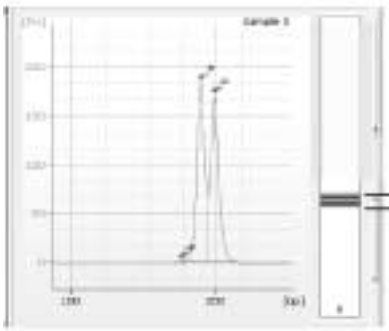
Conclusion

Relapse of the underlying disease continues to be the main cause of failure of allogeneic HSCT in acute leukemia. Thus, improvement in molecular monitoring of donor haematopoietic cells in the early post-transplantation period using high resolution microchip electrophoresis could be useful in predicting the occurrence of increasing recipient chimerism which may herald impending relapse in patients; while the disease burden is still low. This investigational approach may provide useful information for clinicians to select appropriate intervention strategies to ensure successful transplantation. However, validation with more cases needs to be done.



Pre tx

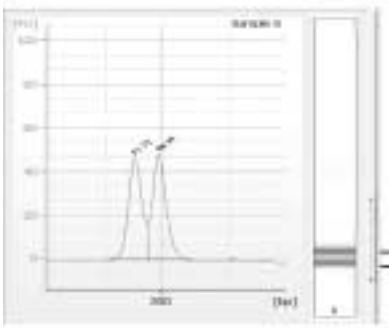
A^{rd} = 199 bp
A^{d} = 192



Donor

A^{rd} = 199 bp
A^{d} = 192 bp

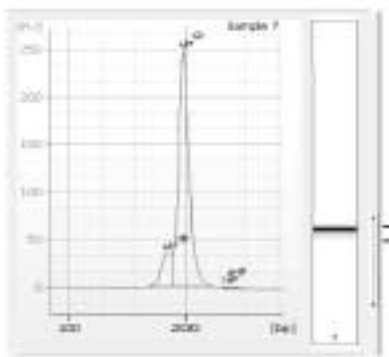
$$100 \times \left[\frac{2 \times A^{d}}{A^{d} + A^{rd}} \right] = \text{\% donor chimerism}$$



Post tx + 22

A^{rd} = 199 bp [FU: 0.97]
A^{d} = 192 bp [FU: 0.94]

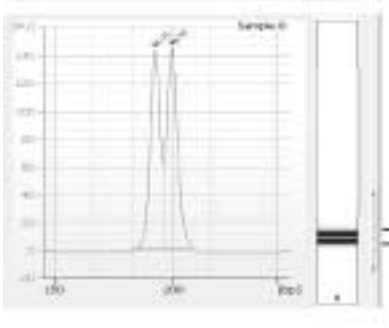
$$100 \times \left[\frac{2 \times 0.94}{0.94 + 0.97} \right] =$$ 98% donor chimerism



Post tx + 3 months

A^{rd} = 199 bp [FU: 4.82]
A^{d} = 192 bp [FU: 0.65]

$$100 \times \left[\frac{2 \times 0.65}{0.65 + 4.82} \right] =$$ 24% donor chimerism



Post tx + 4 months

A^{rd} = 199 bp [FU: 2.96]
A^{d} = 192 bp [FU: 3.03]

$$100 \times \left[\frac{2 \times 3.03}{3.03 + 2.96} \right] =$$ 100% donor chimerism

Figure 3. Schematic representation of patient MW percent donor chimerism calculation. Electropherogram next to the virtual gel image shows informative donor and recipient alleles of TH01STR locus. Peak area of donor specific allele is symbolised = A^{d} and peak area shared by both recipient and donor is symbolised = A^{rd}. The formula to calculate chimerism is based on Nollet *et al*, 2001[15]

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OBESITY AMONG URBAN PRIMARY SCHOOLCHILDREN

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ABSTRACT: Three urban public primary schools in the district of Petaling, Selangor were surveyed for obesity amongst the schoolchildren and factors related to it. The prevalence of obesity amongst primary schoolchildren, with the mean age of 8.91 years was 9.5%. In addition, it was more prevalent among the boys ($p<0.05$) as compared to the girls. However, there was no difference with regards to ethnicity, being breastfed, physical activity, time spent watching television or fast food intake in relation to obesity among these primary schoolchildren. A larger community study is required to determine if other specific factors and dietary energy intake are associated with obesity amongst primary schoolchildren, especially in rural or less urbanised regions. (*JUMMEC 2007; 10(1): 17-20*)

KEYWORDS: Obesity, primary schoolchildren, prevalence, cross-sectional survey

Introduction

Childhood obesity is rapidly increasing worldwide (1,2) and is also increasing in the Asian countries (3). The consequences of childhood obesity include the persistence of obesity into adulthood (4,5), increased risk of diabetes, hyperlipidaemia and cardiovascular disease in later life (6), and negative psychosocial effects (7). Therefore, prevention of obesity is paramount.

Previous studies in developed countries suggested that an increase in energy intake, reduced physical activities and a sedentary lifestyle were factors related to the occurrence of obesity (8,9,10).

In Malaysia, the prevalence of childhood obesity (as defined by the American National Centre for Health Statistics), was 6.0% to 7.8% (11,12). However, in a study by Anuar Zaini *et al*, the prevalence of obesity was 6.3%, using the International Obesity Task Force definition (13,14). The aim of this study was to investigate the prevalence of obesity among primary schoolchildren and factors relating to the occurrence of obesity.

Methods

This study was a cross-sectional survey conducted from January to March 2003 in three primary schools in the district of Petaling in Selangor. Primary schoolchildren aged 7 to 11 years were invited to participate. Participant information sheet, consent form and a structured questionnaire were given to the students to be distributed to their parents. Approval was obtained from the Ministry of Health, Malaysia, the state education department and the headmasters of the selected schools. The three schools selected were publicly funded primary co-education schools. The schoolchildren were selected randomly.

Obesity was defined using a set of sex-specific and age-specific body mass index (BMI) cut-off points, which correspond to an adult BMI of 30 kg/m^2. These cut-off points were derived from BMI centile curves, which was constructed using a mathematical formula (LMS methods) (15).

A pre-tested structured questionnaire was used to record information on socio-demographic details, the mother's breast-feeding practice, student's birth weight, physical and sedentary activities, and the frequency of

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fast food intake. The mother's breastfeeding practice was defined as either exclusive or mixed breastfeeding for at least six months' duration. The physical activities included exercise and involvement in sports. Sedentary activity was based on the time spent watching television. The questionnaire was peer reviewed by sports physicians and a nutritionist. With parental consent, anthropometric assessment of the students was taken by the author (SAH) and two trained research assistants.

Body weight measurement was determined using a SECA 762 mechanical scale (to the nearest 0.5 kg), while the height measurements were (to the nearest 0.5 centimetre) determined using a GIMA (San Donato Milanese, Italy) wall altimeter. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows version 11. Cross-tabulation (χ^2 tests) for categorical variables were used. A *p* value of 0.05 or less was considered significant.

Results

A total of 630 questionnaires were distributed, but only 431 completed questionnaires were returned, giving a response rate of 68.4%. The prevalence of obesity in this study was 9.5%. However, the prevalence was 3.0% when the obesity was defined according to the International Obesity Task Force (14). In this study, 216 (50.1%) schoolchildren were boys and the majority of the participants were of Malay ethnicity. The schoolchildren were aged between 7 and 11 years with the mean of 8.91 years. Table I showed a tabulated summary of the socio-demographic characteristics of the schoolchildren.

There was a difference with regard to gender between the obese and non-obese schoolchildren, where obesity was more prevalent among the boys ($p<0.05$). However, there was no difference noted with regard to ethnicity or within the ethnicity subgroups, being breastfed, physical activities, sedentary activities or frequency of fast food intake (Table 2) between the obese and non-obese schoolchildren.

Discussion

This cross-sectional survey involving 431 schoolchildren between seven and 11 years was conducted in three schools in the district of Petaling in Selangor. Such study is necessary not only to determine the current prevalence of obesity in our schoolchildren but also will allow secular trends to be monitored, particularly those at high risk of developing the problem. More importantly, information gathered from such study will allow better understanding of obesity in schoolchildren by targeting at high-risk groups and will hopefully assist in its prevention.

The prevalence of obesity among primary schoolchildren whose mean age was 8.91 years within the three schools was 9.5%. However, when obesity was defined using the International Obesity Task Force (14), the prevalence was only 3.0%, whereas in a separate study Anuar Zaini *et al* reported a prevalence of 6.3% (13). Their study population was larger, involving only schoolchildren between the age of 9 and 10 years and the majority of the participants were girls (13).

There were significantly more male primary schoolchildren who were obese compared to their female counterparts. This observation was similar to that found by other studies (11,12). Higher prevalence of obesity in male schoolchildren may be associated with their high-risk dietary pattern. However, a more

Table 1. Demographics of the schoolchildren attending urban publicly funded primary schools

Characteristic	n	%
Gender		
Male	216	50.1
Female	215	49.9
Ethnic group		
Malay	269	62.4
Chinese	73	16.9
Indian	72	16.7
Others	17	4
Age		
Mean ± SD (years)	8.91 ± 1.33	
Range (years)	7 to 11	
Breastfeeding practices (non - exclusive)		
At least for 6 months	374	86.6
Never breastfed	57	13.2

thorough study on the amount of dietary energy intake is required to examine this relationship.

This study noted that obesity was equally prevalent in all three major ethnic groups, irrespective of gender, which is similar to that found by another local study (12). In terms of breastfeeding practices, it is comforting to find out that the majority (86.6%) of the mothers were practising breastfeeding on their children during infancy. However, there was no difference between the obese and non-obese groups with regard to this early feeding practice, as shown in other studies (16). In this study, breastfeeding practice included both exclusive and mixed practices. In the other study, the participants were in the younger age groups (i.e. 5 to 6 years old) and studied on exclusive breastfeeding practices (16).

It was noted that there was no association between the frequency of physical activities and obesity. Furthermore, the majority of the primary schoolchildren did not engage in physical activities as recommended by the American Heart Association (17). This present study found no difference in terms of the time spent watching television with obesity, as observed by another study (18). However, a pattern was noted that obesity was less common among those who watch one hour or less of television. Based on self-reported television watching, Crespo *et al* found a positive association between television watching and obesity among girls (9). In this study, the information on the duration of television watching was obtained from the schoolchildren's parents, which could be underestimated.

This study has several limitations. The study population was not representative of the wider Malaysian population. The study was conducted in urban primary schools in a very industrialised and commercial region of Malaysia, where the educational and wealth status of the residents are different from those in many other parts of the country. A community-based study targeting a representative population is likely to provide a better estimation of the size of the problem and identify risk factors for obesity that may be unique to Malaysians.

Table 2. Characteristics of obese schoolchildren in comparison to non-obese schoolchildren

Characteristics of studied group	Obese schoolchildren (N = 41)	Non-obese schoolchildren (N = 390)	χ^2	*p*-value
Gender :				
Male	30 (73.2%)	186 (47.7 %)	$\chi^2 = 9.63$	0.002
Female	11 (26.8%)	204 (52.3%)		
Ethnic group :				
Malay	28 (68.3%)	241 (61.8%)	$\chi^2 = 4.04$	0.257
Chinese	3 (7.3%)	70 (17.9%)		
Indian	7 (17.1%)	65 (16.7%)		
Others	3 (7.3%)	14 (3.6%)		
Breastfeeding experience				
At least for 6 months	35 (85.4%)	339 (86.9%)	$\chi^2 = 0.08$	0.78
Never breastfed	6 (14.6%)	51 (13.1%)		
Physical activities				
< 3 times/week	25 (60.9%)	224 (57.4%)	$\chi^2 = 0.19$	0.66
3 times or more/week	16 (39.1%)	116 (42.6%)		
Time spent watching television/day:				
< 1 hour/day	5 (12.2%)	78 (20.0%)	$\chi^2 = 1.45$	0.23
1 hour and more/day	36 (87.2%)	312 (80.0%)		
Frequency of fast food intake				
< 2 times/week	38 (92.7%)	321 (82.3%)	$\chi^2 = 2.87$	0.09
2 times or more/week	3 (7.3%)	69 (17.7%)		

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EFFECTIVENESS OF 18-HOUR LACTATION MANAGEMENT COURSE ORGANISED BY DISTRICT HEALTH OFFICE FOR HEALTH STAFF

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ABSTRACT: This was a cross-sectional study which attempts to assess the effectiveness of the 18-hour lactation management course organised by Klang District Health Office for its health staff. The course was conducted for three days from 19 to 21 September, 2006 with a total of 18 hours, comprising 15 hours of lectures and three hours of supervised clinical experience. There were a total of 46 participants for the course. The pre- and post-test scores of the participants from the course were used for analysis. This study showed that the mean pre-test versus mean post-test scores were 12.63 and 19.87. The difference in the mean score was statistically significant ($p < 0.001$, 95%CI -8.285, -6.193). The difference was significant for the staff nurse, community nurse and assistant nurse but not for doctors. In conclusion, the 18-hour duration lactation management course was effective at improving the knowledge and skills on breastfeeding management for the health staff. *(JUMMEC 2007; 10(1): 21-24)*

KEYWORDS: Lactation management course, breastfeeding, effectiveness, health staff

Introduction

Breastfeeding has been widely acknowledged as the best means of giving infants a healthy start to life. The world had created a new 'dream product' that would feed and immunise every child on earth, is available everywhere, requires no storage or delivery, and helps mothers to space their births and reduce their risk of cancer, but the world refuses to allow or support its use (1). The advantages of breastfeeding include fulfillment of the nutritional needs of infants, immunological protection, bacteriologically safe, minimal allergic reaction, economically cheap, enhance mother-infant bonding, birth spacing and many others (1-3). Despite great benefits from breastfeeding, the prevalence of exclusive breastfeeding has declined.

Baby Friendly Hospital Initiative (BFHI) was initiated by World Health Organization (WHO)/United Nations Children's Fund (UNICEF) following the Innocenti Declaration on the Protection, Promotion and Support of Breastfeeding on 1 August, 1990. The Declaration called on *'all governments by the year 1995... to ensure that every facility providing maternity services fully practices all ten of the Ten Steps to Successful Breastfeeding'* (4). Each country has to tailor the guidelines for their maternity system and legislation. The 'Ten Steps to Successful Breastfeeding' was the foundation of BFHI. The second step in the 'Ten steps to Successful Breastfeeding' was to train all health staff in skills necessary to implement the breastfeeding policy.

Malaysia has taken up this challenge and currently almost all the government hospitals in Malaysia have achieved the status of Baby Friendly Hospital. The concept has also been extended to involve the health clinics. Government hospitals in Malaysia have been active in achieving and maintaining the Baby Friendly Hospital status. Hospitals were active in providing training to the health staff in knowledge and skills necessary to implement the breastfeeding policy. Traditionally, lactation management courses were organised and conducted in hospitals. Health staff from District Health Office would attend the course in the hospital but in limited numbers. In view of the large number of staff that needed training, Klang District Health Office has organised and conducted the course for its health staff.

Literature search showed no local studies published to look at the effectiveness of the courses conducted. The BFHI criteria recommend that the duration of training should be at least 18 hours in total with a minimum of three hours of supervised clinical experience and cover at least eight steps (5). The

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objective of this study was to assess the effectiveness of the 18-hour lactation management course organised by Klang District Health Office. This paper reports the finding among health staff from the Health Office who attended the course.

Methods

This was a cross-sectional study investigating the effectiveness of the 18-hour lactation management course organised by Klang District Health Office for its health staff. The course was conducted for three days from 19 to 21 September, 2006 with a total of 18 hours, comprising 15 hours of lectures and three hours of supervised clinical experience. The course covered topics on milk production, promoting breastfeeding in pregnancy and beyond, helping mothers in early feeds, evaluation of a feed, on-going support for breastfeeding mothers, early and late breast problems, how to deal with breast 'refusal', low milk production and babies who need special attention. The topics were given by Obstetric & Gynaecology specialists, hospital and health matrons and health sisters. Staff under Klang District Health Office who had never attended the course before were selected. A total of 46 health staff attended and completed the course.

Socio-demographic data of the respondents were included in the answer sheet for the test. Informed consent was obtained from the participants. In this study, the pre- and post-test scores were used for analysis. The set of questions used in the test was based on 'Breastfeeding Management and Promotion in a Baby Friendly Hospital: an 18-hour course for maternity staff' by WHO and UNICEF (6). There were a total of 30 questions and each question carries one mark. The maximum score for the test was 30 marks. The same set of questions was used in the pre- and post-test. The participants were given 30 minutes to answer the questions, in both the pre- and post-test. In Malaysia, the same set of questions were used when conducting the lactation management course.

Data entry and analysis were done using Statistical Package for the Social Sciences (SPSS) version 11.0 for Windows. Paired Student's t-test was conducted on the pre- and post-test scores. Significant level was preset at $p = 0.05$. Confidence interval at 95% was also included, wherever appropriate.

Results

Table 1 showed the socio-demographic data of the study population. Out of the 46 participants, 91.4% (n=42)

Table 1. Socio-demographic data of the study population

Characteristics		mean ± sd	n	%
Age (years)		26.9 ± 0.9		
Gender	Male		0	0
	Female		46	100
Ethnic	Malay		42	91.4
	Chinese		2	4.3
	Indian		2	4.3
Occupation	Doctor		4	8.7
	Staff Nurse		4	8.7
	Community Nurse		36	78.3
	Assistant Nurse		2	4.3
Marital status	Single		16	34.8
	Married		30	65.2
No. of children	0		22	47.8
	1		14	30.4
	2		6	13.0
	3		4	8.8

were Malays while 4.3% (n = 2) were Chinese and another 4.3% (n = 2) were Indians. All the participants were females. The mean age of the population was 26.9 (sd = 0.9 years). The majority of them were married, working as community nurses and have one or no child.

Table 2 showed that in the study population, the mean pre-test score was 12.63 (sd = 3.65) and the mean post-test score was 19.87 (sd = 2.75). Using the 'Paired Student's t-test', there was a significant difference in the mean pre- and post-test score in the study population ($p < 0.001$ and 95% CI -8.285, -6.193).

Table 3 showed the mean pre- and post-test score of the study population by occupation. The highest mean score in both pre- and post-test was among staff nurses (15.75 and 23.50) while the lowest was among assistant nurses (7.50 and 19.00). There was no statistical significant difference in the pre- and post-test score among doctors ($p = 0.063$ and 95% CI -15.77, 0.77). Statistical significant difference were noted among staff nurses ($p < 0.001$ and 95% CI -8.55, -6.95), community nurses ($p < 0.001$ and 95% CI -8.15, -5.74) and assistant nurses ($p = 0.028$ and 95% CI -17.85, -5.15).

Discussion and Conclusion

The results showed that the 18-hour lactation management course was effective at providing knowledge and skills to the health staff. This was apparent by the statistically significant increase in the post-test compared to the pre-test scores. This finding was consistent with The Global Criteria for the WHO/UNICEF Baby Friendly Hospital Initiative (5).

All of the participants in the study were females. This is a likely phenomenon among staff from the health office. Most participants were community nurses. This is understandable because there is a large number of community clinics run by community nurses in the district.

There was a significant difference between the pre- and post-test scores. The course has improved the knowledge and skills among the health staff on breastfeeding management. This study showed that an 18-hour lactation management course improved the knowledge and skills for the health staff. The result

Table 2. Comparing mean pre- and post-test scores of the study population

	Mean pre-test score	**Mean post-test score**	**Mean* difference**	***p*-value**
Pre- & Post-Test Scores	12.63	19.87	-7.239 (95% CI -8.285, -6.193)	< 0.001**

* Statistical testing using paired Student's t-test
** Statistically significance at $p < 0.05$

Table 3. Comparing mean pre- and post-test scores of the study population by occupation

Occupation	**Pre-test score** $\bar{x} \pm$ **sd**	**Post-test score** $\bar{x} \pm$ **sd**	**Statistical significance ***
			***p*-value**
Doctor	14.50 ± 4.04	22.00 ± 1.16	0.063
Staff Nurse	15.75 ± 0.82	23.50 ± 0.58	< 0.001 **
Community Nurse	12.33 ± 0.96	19.28 ± 0.58	< 0.001 **
Assistant Nurse	7.50 ± 0.71	19.00 ± 0.11	0.028 **

* Statistical testing using paired Student's t-test
** Statistical significance at $p < 0.05$

was consistent with studies done by Valdes *et al* (7), Bradley *et al* (8) and the WHO criteria (5). Studies were also done on lactation management courses conducted for more than three days (18 hours). Study by Westphal *et al* on the effects of a three-week course in Brazil among health professionals showed an increase in knowledge and attitude among the participants measured using the pre- and post-course tests (9). Iker and Morgan conducted a study to assess the effects of a four-week part-time training programme for nurses but found no difference in their knowledge or practice on breastfeeding (10).

The mean pre- and post-test score was lowest among assistant nurses. This was expected because their training was very superficial in terms of medical knowledge and they were not exposed to breastfeeding counselling in general. Popkin *et al* conducted a knowledge, attitude and practices survey among health staff in a low-income region of the Philippines and showed that the knowledge on breastfeeding was lowest among the assistant nurses (11). Doctors who attended the course showed no significant improvement in their knowledge on breastfeeding. This finding was contrary to studies done by Valdes *et al* (7) and Wesphal *et al* (9). The inconsistent finding could be attributed to the course because the lectures were prepared and presented for the large number of community nurses.

In conclusion, this study showed that the 18-hour lactation management course organised by Klang District Health Office for its health staff was effective at improving the knowledge and skills on breastfeeding management. Current experience with the BFHI supports that a duration of 18 hours (3 days) is an appropriate minimum length of time for training (5-8). However, training must be compulsory and combined with strong, specific breastfeeding policies to ensure change in hospital and clinic practices. District Health Office could organise lactation management course for the large number of health staff that need training to ensure proper guidance and support for mothers to increase the prevalence of exclusive breastfeeding.

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THE IMPACT OF AN EIGHT-WEEK AEROBIC AND STRENGTH-TRAINING PROGRAMME ON AGILITY AND LEG POWER OF MALAYSIAN NETBALL PLAYERS

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ABSTRACT: The purposes of the study were: (1) to determine the agility and leg power among Malaysian national junior netball players and (2) to determine the impact of eight-week aerobic and strength-training programme on these two variables. A total of 21 netball players from Bukit Jalil Sport School were selected as the subjects in this study. The SEMO Agility Run test was used to determine the agility level while leg power was measured using the Vertical Jump test. Pre-test and post-test results showed no significant differences in the agility and leg power level among the netball players. The mean values for the agility and leg power post-test were 12.59 (SD = 0.56) seconds and 50.24 (SD = 4.90) cm respectively. The pre-test and post-test results for different playing positions recorded the highest improvement in agility and leg power among attacker, followed by centre, and defender. Thus, the training conducted in this study was found to have improved agility and leg power marginally, especially among attacker and centre netball players. *(JUMMEC 2007; 10(1): 25-28)*

KEYWORDS: Agility, leg power, netball player, aerobic training, strength-training

Introduction

The ability to jump and dart about is a very useful skill for netball. This skill would not only help the player lose her opponents, but also confer her better ability in the other aspects of play, such as catching, tapping or snatching the ball (1). In general, the performance should improve with increased agility and leg power. It was reported that better leg strength had contributed to better agility in their subjects (2). In a 3-phase study, it was found that there was an improvement in the jumping ability of Australian elite netball players after training, where the mean jumping height increased by 2 cm (3). The better jumping ability in turn improved the catching of high balls and rebounding. This is inline with the results reported by Cheng *et al* (4) who found that jumping and rebounding training improved muscle strength and this improved the jumping ability of their subjects. This study aimed to determine the agility and leg power in junior Malaysian national netball players and also to assess the impact of an eight-week aerobic and strength-training programme on them. In addition, the study aimed at differentiating the impact of the training on players in the different playing positions in the three broad areas of attack, centre and defence.

Methods and Procedures

Participants

The subjects were all the junior Malaysian national netball players (N = 24) from Bukit Jalil Sport School. Since there were three subjects suffering from serious injury during the training/treatment, only 21 subjects managed to complete all the training/treatment. The range of age of the 21 subjects was between 14 and 18 years old (mean age of 16.12, SD = 1.55 years). Their reported means of height and body weight were 168.11 (SD = 5.31) cm and 62.72 (SD = 5.98) kg, respectively. All have had at least 4.00 (SD = 1.61) years of experience playing netball at inter-state level and above. The number of attack, centre, and defence netball players were 5, 9, and 7 respectively.

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Procedure and Instrumentation

Agility was determined by the SEMO Agility test because the entailed exercises approximated the movements in netball play - darting about and feinting to intercept, pass or receive the ball. The test has good repeatability with an r-value of 0.88 (5). Brower Timing System (Model 22) was used to record the time for the agility test. Meanwhile, the leg power was determined by the Vertical Jump test. The test was reported to have high repeatability and objectivity with both r-values of 0.93 (5). The Digital Indication Jump Meter was the instrument used. When the touch-board is touched, the jump height is displayed on the height indicator. Both the devices were calibrated before the pre- and post-tests.

The experimental design encompassed a span of eight-week training/treatment and consisted of the pre-test and post-test approaches. Before the pre-test, the subjects' agility and leg power ability were measured. After that, they underwent an eight-week training/ treatment programme conducted every Monday, Tuesday, Thursday and Friday mornings (Table 1). At the end of the eight-week training/treatment programme, the post-test was carried out to determine whether there were significant improvements in agility and leg power among the subjects.

Every subject had to abide by the rules, one of which was that she had to be properly attired, e.g. wore a T-shirt and shorts. The uniformity of clothing was to ensure that no subject was advantaged/disadvantaged for the tests (6). The unit of measurement for the agility test was reported in seconds, while the leg power in centimetre (cm). Before the tests, two trials were allowed for the subject to be familiarised with both tests. Each subject was tested twice and the best time for agility and the best height jumped for leg power were taken. Both results were rounded up to the nearest two decimal places in seconds or centimetres. The data were analysed using the Statistical Package for the Social Sciences (SPSS) version 12 software, a widely used statistical package/tool in research.

Training Programme (Experimental Treatment)

Physical training was conducted every Monday, Tuesday, Thursday and Friday in the morning. The afternoon trainings focused on basic netball skills and strategy conducted by the netball coach of the school. Details of the training programme are given in Table 1. The other days were rest days.

Results

Agility

There was no significant improvement in agility of the netball players from the training. The mean agility at pre-test was 12.79 seconds, and while post-test's was 12.59 seconds, which was an improvement of 0.20 seconds. In terms of agility, the centre rank first for the post-test 12.45 (SD = 0.42) seconds, followed by the defence with 12.60 (SD = 0.68) seconds and the attack with 12.75 (SD = 0.51) seconds (Table 2).

Leg Power

There was no significant improvement in leg power of the netball players from the training. The mean leg power result at post-test was only improved by 0.95 cm as compared to pre-test (pre-test 49.29 cm, post-test 50.24 cm). The attack produced the highest jumps of 52.20 (SD = 5.31) cm, followed by the defence 50.60

Table 1. Training programme description

Day	Training	Description
Monday	Strength	• Circuit training with weights (50-70% of 1RM) • Circuit training with weights (80-90% of 1RM)
Tuesday	Aerobic	• Hill run (30-40 minutes at 50-70% THR) • Long distance/cross country run (40 minutes at 50-70% THR)
Thursday	Strength	• Sprinting up a slope for 10, 20 and 30 meters (10% Gradient) • Activities using body weight e.g Burpee, Star Jump, Hopping
Friday	Aerobic	• Long distance/cross country run (40 minutes at 50-70% THR) • Speed Play (30-40 minutes at 50-80% THR) • Short distance interval run (at 50-80% THR)

• Choice of different programmes in different weeks
1RM - 1 Repetition Maximum
THR - Training Heart Rate

(SD = 4.70) cm and the centre 48.00 (SD = 4.86) cm in the post-test (Table 2).

Discussion

Agility

Based on the SEMO Agility Run Norm (6), the players' overall agility was advanced intermediate (agility between 12.99-12.20 seconds). Only five players scored advanced (less than 12.19 seconds) in both the pre- and post-tests. In the post-test, two players completed the SEMO Agility Run circuit in <12 seconds as compared to none in the pre-test. The junior Malaysian netball players' mean agility run of 12.59 (SD = 0.56) seconds (post-test) was better than the Malaysian national netball players agility run norm of 12.89 (SD = 0.61) seconds (7), but was unfavourable as compared to the elite Malaysian netball players' agility run norms of 12.21 (SD = 0.44) seconds (8) (Table 3).

The training improved agility mostly in the attack (0.54 seconds), followed by the centre (0.19 seconds) and the defence (0.03 seconds). Bobo and Yarbrough (9) found that stretching exercises could improve and maintain bodily agility and, in addition, coordination. Besides stretching exercises, better agility was also associated with better leg strength (2). Improvement in these components is likely to improve the overall playing performance of netball players.

Leg Power

Only nine players improved in their leg power after the training. The mean for the post-test 50.24 (SD = 4.90) cm was better than the 47.58 (SD = 4.79) cm reported by Soh, Ruby, Mohd Nor, *et al* (7) for national netball players. However, the leg power results in this study were less than that of elite Malaysian netball players values of 51.82 (SD = 4.33) cm (8). Thus the junior Malaysian netball players were better in leg power compared to the Malaysian norms, but when compared with the elite netball player norms, the junior netball players were found to be less powerful (Table 3).

Table 2. Performance improvement from training by playing position

Playing Position	Agility (seconds)				Leg Power (cm)			
	Pre-test		Post-test		Pre-test		Post-test	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Defence	12.63	0.44	12.60	0.68	51.50	4.84	50.60	4.70
Centre	12.64	0.44	12.45	0.42	46.50	4.09	48.00	4.86
Attack	13.29	0.56	12.75	0.51	48.20	4.92	52.20	5.31
Overall	**12.79**	**0.53**	**12.59**	**0.56**	**49.29**	**4.96**	**50.24**	**4.90**

Table 3. Comparison in agility and leg power among junior, national and elite netball players in Malaysia

Test	Junior Netball Players		National Netball Players[7]		Elite Netball Players[8]	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Agility (sec)	12.59	0.56	12.89	0.61	12.21	0.44
Leg Power (cm)	50.24	4.90	47.58	4.79	51.82	4.33

Source:
[7] Soh KG, Ruby H, Mohd Nor' CN, *et al.* (2000)
[8] Soh KG, Ruby H, Mohd Nor' CN, *et al.* (2003)

The training improved leg power mostly in the attack (increased by 4.00 cm) and centre (increased by 1.50 cm) netball players. However, there was a decrease in leg power performance among the defence netball players (decreased by 0.90 cm). The decrease in the leg power might be due to the defence netball players having better initial leg strength ability before the start of training, as compared to the attack and centre players. According to Sharkey (10), a better leg strength would increase the jumping height. However, the ability to improve the jumping height was dependent on the athlete's initial leg strength before the training. The jumping and rebounding types of training were proven to improve muscle strength and these, in turn, improved the jumping ability (4). However, there are also other factors that could determine the progress made in training to improve jumping. These factors are such as overall strength and maximum force rate development, power-to-body mass ratio, ability to flex the muscles, and movement coordination (11).

Conclusion

The eight-week aerobic and strength-training programme was found to be inadequate to improve agility and leg power in the netball players. The junior netball players were found to be less agile as compared to the elite Malaysian netball players and reported to have only moderate agility level as compared to the SEMO Agility Run Norm (before and after training). This could be due to several factors, such as the lack of emphasis on agility in their training as their programme was more focused on overall fitness. Hence, to improve their agility and leg power, specific agility and leg power exercises would have to be incorporated. Such exercises will enhance their movements and make them more efficient, as a result of which their agility and leg power will improve (5,12,13).

Acknowledgements

The authors wish to thank the Malaysian Netball Association (MNA) for the support in this study. Gratitude is also expressed to the netball coach, Miss Choo KL, and the subjects who participated in this study. Thanks are also due to Associate Professor Zaliha Omar and staff of Faculty of Medicine, University of Malaya for their technical and material support.

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THE LEVEL OF PHYSICAL ACTIVITIES AMONGST ELDERLY IN A COMMUNITY

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ABSTRACT: Little is known of Malaysian older people's participation in physical activities, and the purpose of this pilot study is to explore their participation and the barriers. A self-administered questionnaire was given to 80 eligible respondents at the Kuala Lumpur Health Clinic of which 70 responded. Thirty-six (51.4%) were males and 34 (48.6%) were females. There were 26 (37.1%) Malays, 20 (28.6%) Chinese, 18 (25.7%) Indians and 6 (8.6%) of other ethnic groups. Forty (57.1%) took part in some form of physical activities and the remaining 30 (42.9%) reported no participation at all. The Chinese participated actively in physical activities (90%), followed by Indians (66.7%) and Malays (30.8%). The five common activities were walking (60%), tai chi (20%), gardening (12.5%), stretching (2.5%) and cycling (5.0%). Identified barriers to physical activities were lack of time (26.7%), having health problems (26.7%), was already fit (26.7%), no companion to exercise with (13.3%) and no exercise knowledge (6.7%). These findings indicated that emphasis should be given to the females and the Malay ethnic group when planning physical activity education for the older people as they were identified to be the least active groups. *(JUMMEC 2007; 10(1): 29-33)*

KEYWORDS: physical activities, geriatric, older persons

Introduction

Global growing number of elderly population and the emerging social and health consequences of ageing is a major challenge, especially to the developing countries(1).The number of elderly people (those aged 65 or older) in less developed countries is expected to increase from 249 million to 690 million between 2000 and 2030 (2). Furthermore, because the elderly are at high risk for disease and disability, this aging population will place urgent demands on the healthcare systems of developing-countries, most of which are ill-prepared for such demands (2).

In Malaysia, ageing has also become an important issue because of dramatic changes in life expectancy, as a result of socioeconomic development and advancement in medical services. In 2000, the life expectancy at birth was 70 to 72 years for males and 74 years for females, compared to 68 to 70 years for males and 70 to 72 years for females in 1996 (3). At present, there are approximately one million elderly people in Malaysia, which is 6.1% of the total population. If life expectancy continues to increase, it is estimated that by the year 2020, the total ageing population will be 3.8 millions that is 11.3 % of the total Malaysian population (3).

As people are living longer, there is a need to develop health-promoting strategies to cope with the growing societal consequences of ageing. Increasing age is associated with increasing health problems, disability and loss of independence (4,5). If the incidence of such consequences is not controlled, the costs in treating elderly people with health problems will continue to increase (6).

A number of measures have been identified to help maintain older people's health and quality of life (7). Simple measures include using the impact of modifiable influences such as diet, environmental elements and physical activity (4). The benefits of physical activity, defined as 'any bodily movement produced by the contraction of skeletal muscles' (8) in improving and maintaining health and well-being of elderly persons have been well documented (9,10,11). However, little

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is known about the participation of older population in these recommended activities, particularly in Malaysia. The aims of this study are to explore patterns of participation in physical activities within a group of Malaysian older people and to determine whether the patterns of participation in physical activities is related to the demographic characteristics, that is age, gender and ethnicity.

Methods

This study is a non-experimental descriptive study using a self-administered questionnaire. The questionnaire comprised two parts: Part A comprising demographic characteristics of the respondents and Part B looks into the patterns of physical activity participation. Questions in the questionnaires were adapted from Zutphen Physical Activity Questionnaire (8) and CHAMPS Activities Questionnaires for Older Adults (12) which have been tested for their validity and found to have good inter-rater and intra-rater reliability value. A pilot study on the questionnaire was carried out on ten elderly, who responded well to the questionnaire, indicating reliability of the questions asked. Further improvement was made on the questions prior to using it in this study. The questions included in the questionnaire were those considered to be relevant to the lifestyle of the elderly as they match the cultural activities of the Malaysian society.

The selected demographic characteristics were age, gender and ethnicity. These data were collected to enable comparison in physical activity patterns between the subgroups. As for the questions pertaining to patterns of physical activity participation, the respondents were first asked to acknowledge whether they have participated in any physical activities. Those who answered 'NO' were asked to give their main reason for no participation and those who answered 'YES' were required to state the type of activities they performed most. Questionnaire was tested for clarity prior to conducting the actual survey.

Analysis was done by subgroups using descriptive statistics, mainly frequencies and cross tabulations by using the Statistical Package for the Social Sciences (SPSS). Comparisons between the subgroups were made to study the differences in physical activity patterns according to age, gender and ethnicity.

Study Location

The study was conducted at the Kuala Lumpur Health Clinic, which is the main health clinic for residents from the Klang Valley. A letter informing about the study and requesting for permission to carry out the study was sent to the Director of Kuala Lumpur Hospital, in which the study was conducted. Seventy subjects were enrolled in the study using a convenience sampling method. In Malaysia, older people are defined as those aged 60 and above (3); therefore the lowest age limit for participants was 60. Exclusion criteria were inability to read and write due to whatever reason and poor mental capacity. Consent of the subjects was inferred by voluntary completion and return of the survey questionnaires. The anonymity of the respondents was protected by not having their names, contact addresses and any identification numbers on the questionnaires. This is to ensure that the respondents reported their experiences without being prejudiced.

Results

Out of a total of 80 questionnaires distributed, 70 questionnaires (87.5%) were returned, while those who did not respond were not able to write or were rushing off immediately from the centre to go home. Among the participants, 51.4% (n = 36) were males and the remaining 48.6% (n = 34) were females; 37.1% were Malays, 28.6% Chinese and 25.7% Indians, and 8.6% other ethnic groups.

About 57% claimed that they took part in physical activities and another 42.9% reported no participation in any physical activities.

In the non-physically active group, 23.3% were those aged between 60 and 64 years similar to those aged 65 and 69 years. Eight (26.7%) were aged 70-74 years. Six (20%) were aged 75 and 79 years and two (6.6 %) were above 80 years. The proportion that reported participation in physical activities was higher than those who reported not actively participating for all age groups except for the age groups of 70-74 and 75-79 years.

In terms of gender, a total of 60 % (n = 24) who reported participation in physical activities were males and 40% (n = 16) were females, whereas those who reported no participation in physical activities were 40% (n = 12) men and 60% (n = 18) women.

Among the different ethnic groups, the highest score of participation was 45% (n = 18) Chinese followed by 30% (n = 12) Indians, 20% (n = 8) Malays and 5% (n = 2) "others". Interestingly, when 'no participation in physical activity' was observed, the Malays showed the biggest percentage, followed by Indians, and least among Chinese.

Table 1. Physical activities among active participants

Characteristics	n(%)
Age (years)	
60-64	11 (27.5)
65-69	11 (27.5)
70-74	9 (22.5)
75-79	6 (15)
>=80	3 (7.5)
Gender	
Female	16 (40)
Male	24 (60)
Ethnicity	
Malay	8 (20)
Chinese	18 (45)
Indian	12 (30)
Others	2 (5)

In Figure 1, the types of physical activities performed among those who participated in physical activities included walking 60% (n = 24), tai chi 20% (n = 8), gardening 12.5% (n = 5), stretching 2.5% (n = 1) and bicycling 5.0% (n = 2).

In comparison, the reasons for barriers to physical activities among those who did not perform physical activities were 26.7% (n = 8) lack of time, 26.7% (n = 8) having 'health problems', 26.7% (n = 8) 'is already fit', 13.3% (n = 4) having no companion to exercise, and lastly 6.7% (n = 2) commented that they have no exercise knowledge (Figure 2).

Discussion

Out of 70 participants, 57.1% reported participation in physical activities and another 42.9% reported no participation indicating that the proportion of participants who were physically active was slightly higher than those who were inactive. This result is comparable with the findings by DiPasquale-Davis *et al* (13), who reported that a higher proportion of those who were physically active (60%) compared to those who were inactive among a group of older Filipino. This shows that a higher proportion of the older people practise an active lifestyle and lower proportion have a sedentary lifestyle though the sample size of this study is too small to generalise the lifestyle of Malaysian elderly participation in physical activities.

Participation in physical activities was higher in men than women, similar to the findings by USHHS (14) that reported women were more likely to report no physical activity than men. Culturally, the Malaysian older women, regardless of their age, are more involved in housework and childcare as compared to men. As these activities are energy consuming, women, being naturally less energetic than men (15) might not have extra energy to partake in any leisure time physical activity. Another possible reason is that the older Malaysian women are more 'indoor' and are less likely to involve in social activities compared to men. Socialisation exposes a person to knowledge on healthy lifestyle practices better, particularly when active interaction occurs with other members in the society who lead an active lifestyle.

In terms of ethnicity, the participation in physical activities was highest among the Chinese, while the Malays demonstrated the highest proportion of inactivity. The culture of these three main ethnic groups are different. Therefore, this finding supports the

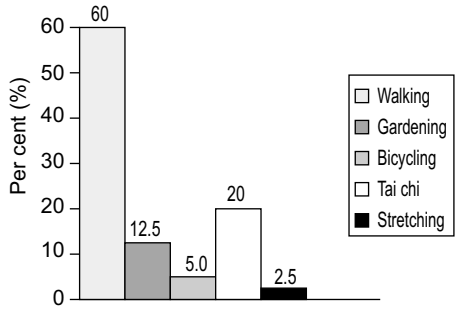

Figure 1. Common types of physical activities performed

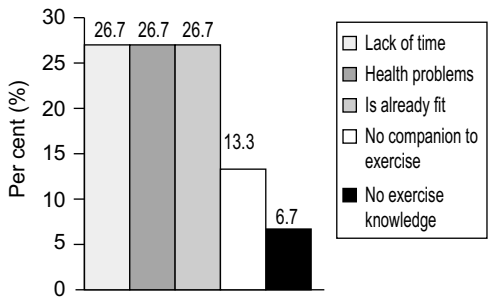

Figure 2. Common barriers to physical activities

statement that health behaviours vary among and within cultural groups (13). The Chinese might appreciate health more than Indians and Malays for a reason that is not well-understood. Another possible reason is, being Muslim, the Malays perform their prayers five times a day; each session involves repetitive concentric and eccentric movements of the legs. This results in moderate physical exercise, to every muscle in the body. Some muscles contract isometrically and some contract in approximation or isotonically. The energy needed for the muscle metabolism increases during the performance of Salat (formal worship performed five times each day), resulting in a relative deficiency of oxygen and muscle nutrients. In turn, this deficiency causes vasodilation- an increase in the caliber of blood vessels, thereby, allowing blood to flow easily back to the heart. The temporarily increased load on the heart acts to strengthen the heart muscle and to improve the circulation within the heart muscle (16). As a result, the Malays might regard themselves as already physically fit, therefore do not require exercise or physical activity.

In this study, the participants reported five types of activities commonly performed that is walking, tai chi, gardening, stretching and bicycling. Walking was the most commonly reported physical activity consistent with studies done in other countries (14,17,18). In Malaysia, the Healthy Lifestyle Campaign places great emphasis on walking as a recommended activity towards health gains. Furthermore, walking was given wide coverage by the mass media in the previous health write-ups. These would have probably influenced the choice of physical activities in this study group. Studies have shown that the older people perceived ability to maintain walking as a sign of successful ageing (17). If this is also true among the older Malaysians, this could be another reason for choosing walking exercise, as it is only this way that their walking ability could be maintained.

A number of reasons were reported for no participation in physical activities. The most commonly reported reasons were lack of time, health problems and the perception that one is fit and no companion. These results are comparable with many studies that looked into barriers for no participation in physical activity among the older people (16,17,19). The proportion that reported 'no exercise knowledge' is small, indicating that generally, subjects in this study possessed knowledge on physical activity. This might be due to the existence of the Health Education Unit at the Kuala Lumpur Health Clinic, which runs health education talks on a regular basis; therefore providing opportunity for the participants to gain knowledge on physical activities. This result also supports the findings by Goggin and Morrow (20) who reported that older people are aware of the health benefits of physical activities though a high proportion of them did not participate in this activity.

Conclusion

Information generated from this study can be used as baseline in reviewing health education programme for the elderly in Kuala Lumpur Health Clinic. The findings indicated that emphasis should be given to the females and the Malay ethnic group when planning physical activity education for the older people as they are identified as the least active groups in the study. Strategies should include ways to overcome barriers; preferably tailored individually since the perceived barriers differ across the sub-groups. It is also important to educate the older people on the current recommendation of physical activity to ensure that the older people benefit optimally from their physical activity practices. The selection of participants is non-random, therefore it is inadequate to generalise on the physical activity amongst elderly in the Malaysian population. However, since this study is a pilot, further research should be carried out in a population of elderly, both in rural and urban communities.

Future studies should also look into the reasons why different people choose different activity and its relation to their functional status to ensure better understanding of the patterns of physical activities among the older people. By doing so, education on physical activities for the older people can be delivered more effectively by the involved health care providers.

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CARBIMAZOLE-RELATED AGRANULOCYTOSIS IN PREGNANCY – A CASE REPORT

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ABSTRACT: We report a 33-year-old Malay lady who presented with fever, tonsillitis and pharyngitis a month after initiation of antithyroid therapy (carbimazole 15 mg tds) for thyrotoxicosis by her general practitioner. She was still clinically and biochemically thyrotoxic but not in thyroid storm. At that time, she was also confirmed to be four weeks pregnant. Her full blood count revealed neutropaenia with an absolute neutrophil count of 0.036×10^9/L. Bone marrow aspirate and trephine were compatible with carbimazole-related agranulocytosis. Carbimazole was discontinued and she was given broad spectrum antibiotics and Granulocyte Colony Stimulating Factor (GCSF), to which she responded. Verapamil was used for symptomatic heart rate control instead of beta-blockers as she had a history of bronchial asthma. The patient subsequently opted for termination of pregnancy after which she was given radioactive iodine I^{131} (10 mCi) for definitive therapy of her thyrotoxicosis. In conclusion, carbimazole-related agranulocytosis is an important entity to recognise and treat early to prevent morbidity and mortality. Termination of pregnancy was carried out as the treatment given during the episode of agranulocytosis may have negative effects on foetal viability and growth. *(JUMMEC 2007; 10(1): 34-38)*

KEYWORDS: Thyrotoxicosis, carbimazole, agranulocytosis, neutropaenia, pregnancy, granulocyte colony stimulating factor

Introduction

Hyperthyroidism in pregnancy is relatively rare, occurring in 0.2% of pregnancies in the US, with the most common cause being pre-existing Graves' disease (1-4). Uncontrolled hyperthyroidism can adversely affect not only the mother's health, but can cause congenital abnormalities, foetal goitre, thyrotoxicosis, neonatal Graves' disease, and an increase in foetal mortality (3).

Medical treatment for thyrotoxicosis consists of carbimazole (methimazole) or propylthiouracil. In the US, propylthiouracil is more popular whereas in the UK and Europe, carbimazole is more frequently used. Aplasia cutis has been described in about 20 infants exposed *in utero* to methimazole (carbimazole) (5). The risk of occurrence when using this medication is unknown, but no adverse reactions to the foetus have been described with the use of propylthiouracil. Thus, propylthiouracil is preferred to carbimazole (methimazole) in pregnancy (5).

Carbimazole is a prototype drug in the thionamide group, which is commonly used for the treatment of thyrotoxicosis. It is very effective in the treatment of thyrotoxicosis but, like any other drug, it has side-effects, namely, fever, skin rashes, arthralgia and hepatitis. Carbimazole-related agranulocytosis is rare with an incidence of 0.3%-0.6% but mortality is less than 1 in 10,000 (6) treated patients as compared to 20% in the past (7). Recent studies have shown that the mechanism of antithyroid drug-related agranulocytosis is more of an immunological phenomenon, rather than a direct toxic effect of the antithyroid drugs (ATD) (8). Patients who develop agranulocytosis are susceptible to a variety of infections, some of which are potentially fatal.

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In short, carbimazole-related agranulocytosis is associated with significant morbidity and mortality. This adverse effect is more complicated in a pregnant individual. Here, we are not only concerned about the thyroid status of the mother but also the effects of the drugs for example, GCSF on the foetus while managing the agranulocytosis.

We would like to illustrate the above by reporting a case of a pregnant patient with thyrotoxicosis who developed carbimazole-related agranulocytosis.

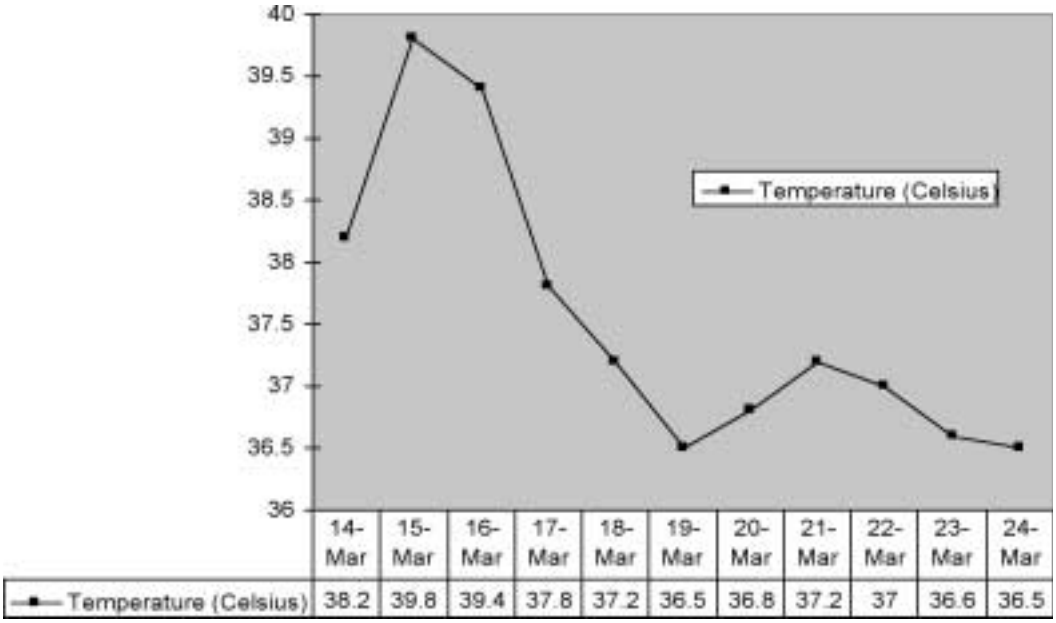
Case Report

A 33-year-old woman with a background history of bronchial asthma presented to the University Malaya Medical Centre with a one-week history of fever, vomiting and diarrhoea. This was preceded by a non-resolving sore throat for a month. At that time, she had been diagnosed by her general practitioner to have thyrotoxicosis, having presented with the classical features, i.e. tremors, palpitation, heat intolerance and weight loss of 12 kg over the previous five months. She was started on carbimazole 15 mg tds.

Clinical examination revealed that she was febrile (38.2°C) (Figure 1a), tachycardic (120 beats/min) and tremulous with an underlying small diffuse goitre. She was not, however, in thyroid storm. There was also enlargement of the tonsils with white exudates.

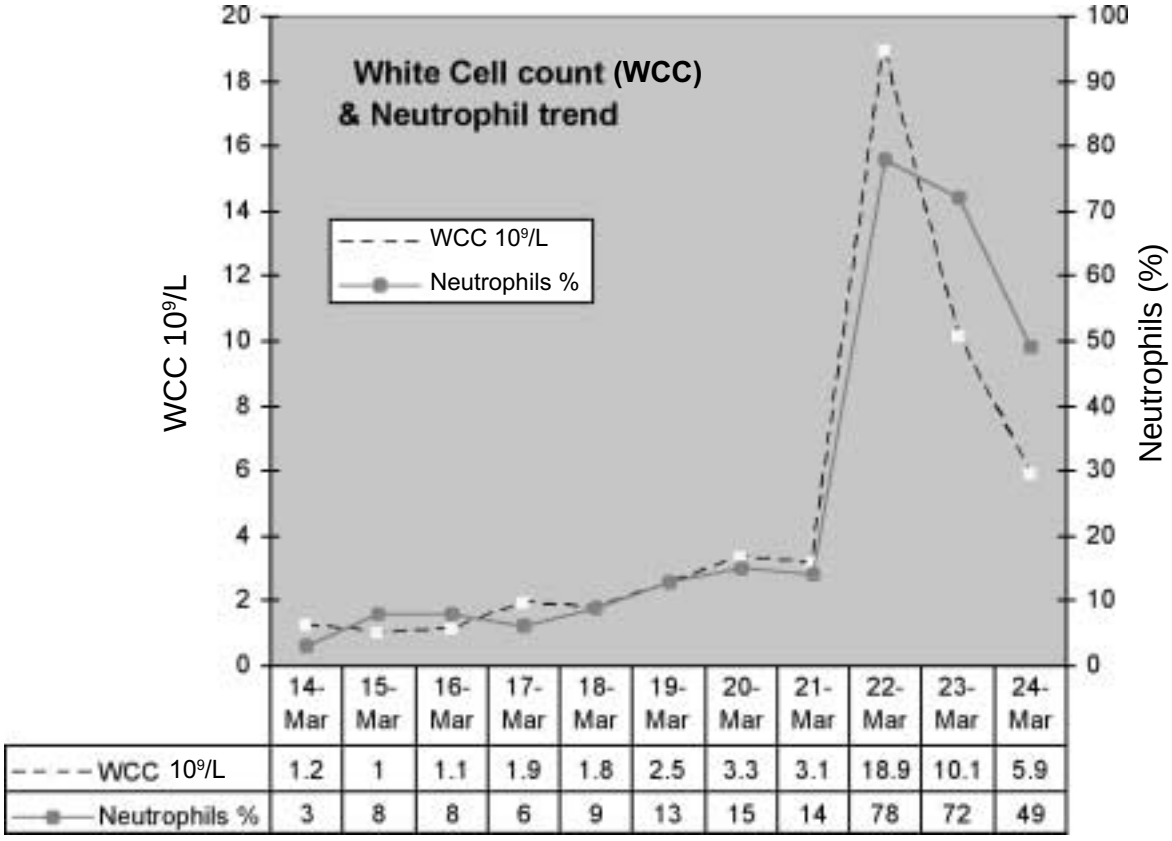
White blood cell count on admission was 1.2×10^9/L with an absolute neutrophil count of 0.036×10^9/L (Figure 1b). Bone marrow examination showed mildly depressed granulopoiesis with maturation arrest at the myelocyte stage in keeping with drug-induced agranulocytosis (Slide 1). At that time, her free thyroxine was 40.4 pmol/L and Thyroid Stimulating Hormone (TSH) was < 0.01 mIU/mL (Figure 2). She was also found to be four weeks' pregnant based on her account on a period of amenorrhoea and this was confirmed by a positive urine pregnancy test and an elevated serum Beta Human Chorionic Gonadotrophin. Transvaginal ultrasound also confirmed an intrauterine yolk sac and right corpus luteal cyst. She was gravida 5, para 2 with 2 previous abortions.

She was started on verapamil 40 mg bd for symptomatic control of her heart rate. Beta-blockers were avoided as she had a past history of bronchial asthma. She was also treated with intravenous piperacillin-tazobactam 4.5 g three times daily empirically for febrile neutropaenia. Her fever resolved after three days of antibiotics. As her white cell counts failed to improve, she was given 300 μg of subcutaneous GCSF. Her neutrophil count rose to more than 0.5×10^9/L, 5 days after GCSF which corresponds to 9 days after stopping carbimazole. The white cell count continued to rise to 1.9×10^9/L and finally reached 5.9×10^9/L (Absolute Neutrophil Count [ANC] of 49%) (Figure 1b). As all blood and urinary cultures were negative, the antibiotic was stopped after one week. The patient's condition gradually improved but she remained thyrotoxic.



	14-Mar	15-Mar	16-Mar	17-Mar	18-Mar	19-Mar	20-Mar	21-Mar	22-Mar	23-Mar	24-Mar
Temperature (Celsius)	38.2	39.8	39.4	37.8	37.2	36.5	36.8	37.2	37	36.6	36.5

Figure 1a. Temperature profile of patient

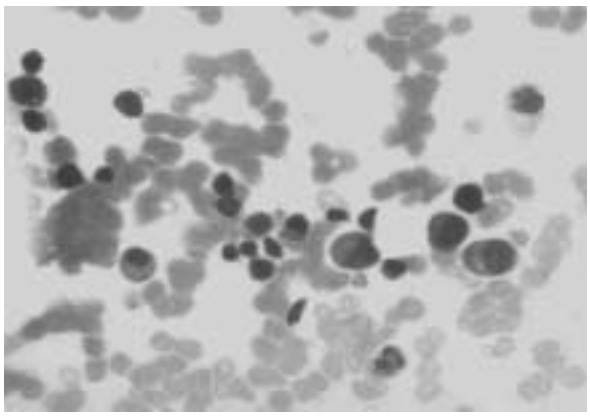


	14-Mar	15-Mar	16-Mar	17-Mar	18-Mar	19-Mar	20-Mar	21-Mar	22-Mar	23-Mar	24-Mar
WCC 10^9/L	1.2	1	1.1	1.9	1.8	2.5	3.3	3.1	18.9	10.1	5.9
Neutrophils %	3	8	8	6	9	13	15	14	78	72	49

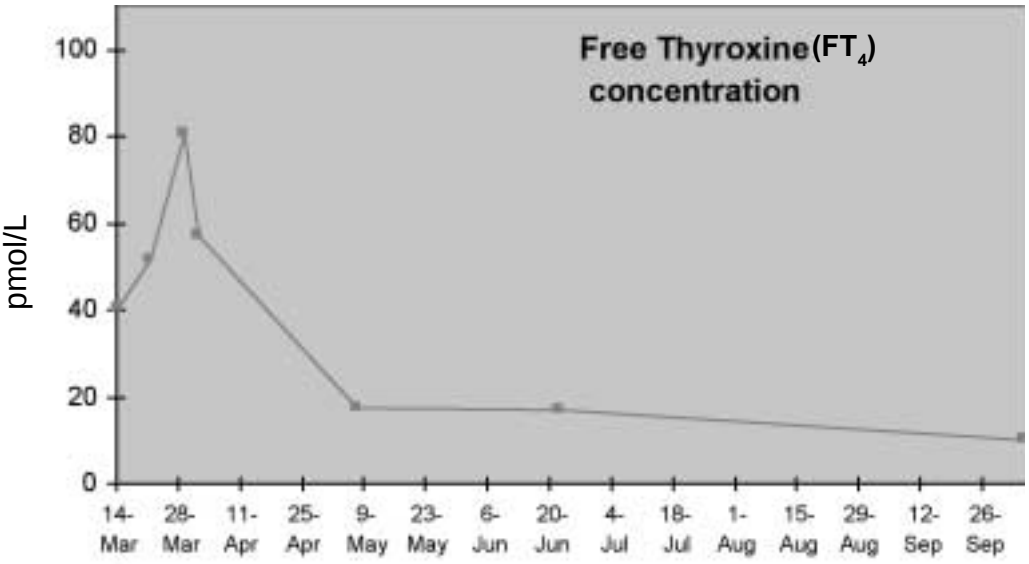
Figure 1b. White Cell count and neutrophil trend of patient

Subsequent management was comprehensively discussed by a multidisciplinary team that included endocrine, obstetrics and nuclear medicine divisions, together with the patient and her husband. Issues discussed included the potential risks of recurrent agranulocytosis with reinstitution of thionamide therapy, the risk of untreated and uncontrolled thyrotoxicosis to the mother and foetus in pregnancy. The effects of the various treatment options on the foetus were also discussed – for example, GCSF is known to cause organogenesis associated with increased foetal resorption, genitourinary bleeding, developmental abnormalities and decreased body weight if administered to pregnant rabbits at doses of 80 mcg/kg/day (9). However, since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of GCSF on the developing human foetus or the reproductive capacity of the mother is unknown.

Radioactive iodine, on the other hand, being the most widely recommended definitive treatment with thyroidectomy being the second (but widely used) choice, could cross the placenta and destroy normal thyroid cells in the baby (10) as the effects of radioiodine which has a half life of up to nine days, may persist indefinitely (11). Therefore, the patient finally, opted for termination of pregnancy when she was stabilised followed by radioactive iodine ablative therapy (10 mCi), which she underwent uneventfully a month after the termination. She was hospitalised during the radioactive iodine ablative therapy for a week as it may precipitate thyroid storm. Verapamil was continued to control her heart rate until she became euthyroid. At follow-up six months later, she was hypothyroid requiring thyroxine replacement.



Slide 1. Histology of bone marrow with depressed granulopoiesis and maturation arrest at the myelocyte stage



	14-Mar	21-Mar	29-Mar	1-Apr	7-May	22-Jun	5-Oct
fT4 pmol/L	40.4	51.4	80.5	57.1	17.4	17.2	9.9
TSH	<0.01	<0.01	<0.01	<0.01	0.01	<0.01	3.82

Figure 2. Free Thyroxine concentration

Discussion

This was a rare and complicated case of antithyroid drug-related agranulocytosis as it occurred in a pregnant lady who had bronchial asthma. The duration of treatment with carbimazole to the onset of agranulocytosis is important to note. Agranulocytosis (ANC < 0.5 x 10^9/L) is an idiosyncratic reaction that can occur anytime during treatment with thionamides but usually happens within 1- 2 months after starting treatment (12). However, agranulocytosis occasionally can develop even though the total white blood cell count remains within normal range and therefore, it is important to perform differential counts (13).

Recognition of early symptoms is the first step to diagnosis. A history of fever a month after commencing carbimazole with an absolute neutrophil count of 0.5 x 10^9/L and bone marrow histology of mildly depressed granulopoiesis with maturation arrest at the myelocyte stage is consistent with carbimazole-related agranulocytosis. Although it is known that relative lymphocytosis and relative monocytosis, with a normal or slightly low total white cell count, constitute the characteristic blood findings of Graves' disease; significant pancytopaenia with leukocyte counts under 3×10^{-9}/L and neutrophils under 2×10^{-9}/L occasionally occurs, and if unrelated to drug therapy, tends to recover during treatment (14). With regard to this case, the white cell count did not improve during carbimazole therapy. Upon withdrawal of carbimazole the white cell count improved. As such, we therefore concluded that neutropaenia was due to carbimazole rather than the disease itself.

The infection associated with carbimazole-induced agranulocytosis usually starts from the oropharynx, either acute pharyngitis or tonsillitis. In some clinical studies, the most commonly isolated microorganism is *Pseudomonas aeruginosa* (8).

The management of carbimazole-induced agranulocytosis has evolved over the years. The introduction of GCSF has led to quicker recovery of granulocytes. Tajiri J, Noguchi S, Murakami N (15) published a prospective study on the use of GCSF measurements four hours after injections of GCSF. It concluded that GCSF measurements four hours post-administration were useful for detecting recovery from ATD-induced granulocytopaenia or agranulocytosis and for predicting disease severity (15). Hence, this implies the speedy action of GCSF in reducing the incidence of fatal complications (12).

The offending drug needs to be stopped immediately. Broad spectrum antibiotics with pseudomonal coverage have to be started empirically.

Because of her past history of bronchial asthma, beta-blockers could not be given to alleviate her adrenergic symptoms. Verapamil, a calcium channel blockers were given to control her heart rate as an alternative.

Although secondary amenorrhoea is a common feature of thyrotoxicosis, and this patient reported delayed menses, testing for pregnancy revealed that she was pregnant.

Termination of pregnancy was contemplated as GCSF's effect on human pregnancy is unknown. Although piperacillin and tazobactam were not teratogenic in animal studies, both antibiotics cross the human placenta. Their effects on pregnancy in humans are also unknown (16). As for verapamil, it readily crosses the placenta and has been shown to cause foetal bradycardia, heart block, depression of contractility, and hypotension (17).

Termination of pregnancy is preferably done in the first trimester as the risk of bleeding is lower. After the termination, definitive therapy for her thyrotoxicosis was discussed. The patient opted for radioactive iodine (10 mCi) after termination of pregnancy. The treatment of thyrotoxicosis with radioactive iodine is much more efficacious than medical or surgical modalities. Furthermore, it is by far the most cost-effective and has no harmful effects (18). Surgery, on the other hand, is currently only employed in a minority of patients. Indications for surgery include thyrotoxic individuals who are allergic to thionamides and unable to take radioiodine because of pregnancy, youth, massive thyromegaly with compressive symptoms or personal choice (19). Its limited indication is due to a somewhat higher incidence of recurrent laryngeal nerve damage and permanent hypoparathyroidism (20). Propylthiouracil was not considered as there is cross reactivity of as high as 50 per cent with carbimazole (21).

In summary, patients ought to be informed of the side effects of carbimazole – in particular agranulocytosis. Although it is rare, patients should be told to look out for early warning signs in terms of symptoms and duration of therapy in order to seek early and prompt treatment. Agranulocytosis is life-threatening but treatable within the window of opportunity.

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