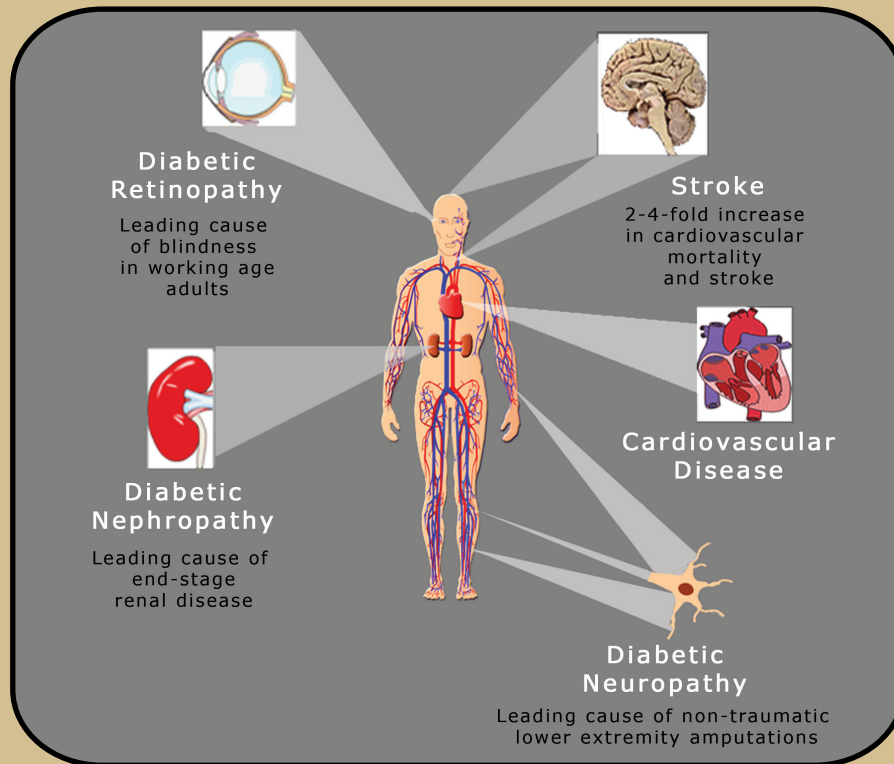


JUMMEC



Volume 12 Number 2 2009

This journal is indexed/abstracted by Elsevier (Scopus) and MyAIS

**Journal of the
University of Malaya
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**UNIVERSITI
MALAYA**

December 2009
Volume 12 Number 2

JUMMEC

Journal of the University of Malaya Medical Centre



**UNIVERSITI
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JUMMEC

Journal of the University of Malaya Medical Centre

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2009

CONTENTS

Guest Editorial

- Early Detection, Appropriate Management – Ensure A Legacy Of Good Health44
Amir SK

Review

- Diabetes Control – the Legacy of a Memory47
Vijay AP, Chan SP

Original Articles

- Ventricular Dyssynchrony is Common Among Heart Failure Patients
with Narrow QRS Complex57
*Yaakob ZH, Syed Tamin S, Nik Zainal NH, Chee KH, Chong WP, Hashim NE,
Singh R, Zainal Abidin I, Haron H, Wan Ahmad WA*

- A Randomized Controlled Study Comparing Subcutaneous Pethidine
with Oral Diclofenac for Pain Relief after Caesarean Section63
Marzida M

- Challenge and Support for Breastfeeding in Highly Motivated Malaysian Mothers70
Nazatul SB, Ruby H

- Construction and Validation of a Malay Version of the Overactive Bladder Screener
for Assessing Urinary Tract Symptoms in a Malaysian Population74
Muhilan AP, S Sivaprakasam, Dublin N, S Rampal, Razack AH, Thun TH, Chua CB

- Ensuring Patient Safety in the New Operating Theatre of UMMC Trauma Centre;
an Anaesthesiologist Novice Experience83
Mamat M, Chan L

Case Reports

- Carbimazole-induced Aplastic Anaemia – a Case Report92
Vijay AP, Lim SS, Tan ATB, Rokiah P, Chan SP

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The Journal of University of Malaya Medical Centre (*JUMMEC*) is published two times a year by the University of Malaya Medical Centre.

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Cover

Complications of Diabetes; adapted from the graphical image from <http://www.niddk.nih.gov/health/diabetes/pubs/dmstats/dmstats.htm#comp>. Accessed 1 May, 2001.

Printed by

Touch Graphic, No. 21-1, Jalan Wangsa Delima 10, D'Wangsa Maju, Kuala Lumpur, Malaysia.

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EARLY DETECTION, APPROPRIATE MANAGEMENT – ENSURE A LEGACY OF GOOD HEALTH

Amir SK

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The current volume of JUMMEC contains a wide spectrum of health topics highlighting the importance of controlling metabolic factors in diabetes, selection of heart failure patients for innovative treatment, early postoperative analgesia, testing of a translated screener for urinary tract problems, problems when commissioning a new operating theatre and breastfeeding issues.

Chronic diseases such as heart disease, and diabetes account for a large proportion of health care expenditure and these can be prevented (or at least delayed) by healthier diets, improved physical fitness and, in the case of the former, no tobacco use. Screening tests exist for many chronic diseases which can detect the disease while they are still asymptomatic. Early diagnosis and appropriate treatment of disease may lead to cures and better survival. Type 2 diabetes mellitus (T2DM) is an ideal disease for early detection with simple measurement of timed blood glucose. Epidemiological studies on T2DM and the related metabolic syndrome have consistently detected undiagnosed individuals for every known individual with diabetes. There are known risk factors that increase the likelihood of developing T2DM with family history, excess body weight, and previous gestational diabetes mellitus being prominent. T2DM is an important health care problem as it can lead to long term microvascular as well as cardiovascular complications.

The review article by Vijay and Chan examines the link between glycaemia and complications (1). For those treating individuals with diabetes, their intuition would make them pursue normalisation of the blood sugar. It was formally confirmed in the 1990s that in type 1 and 2 DM, DCCT and UKPDS respectively, reducing glycaemia leads to improvements in microvascular outcome. The picture for cardiovascular disease benefit was less clear, with several unanswered questions like level of glycated haemoglobin (HbA1c) lowering needed, safety of rapid lowering of HbA1c in all individuals and whether all glucose lowering agents are safe and efficacious. Coronary heart disease is the major cause of morbidity and mortality in patients with T2DM. Vijay and Chan mentioned three trials with largely negative CV benefits, namely ACCORD, ADVANCE and VADT, where the studies have not

demonstrated a benefit from intensive glycaemic control on primary CVD outcomes. Hypoglycaemia was worse in the intensive arm of ACCORD, a study stopped because of excess mortality in the intensive group. A recent meta-analysis looking at UKPDS, ADVANCE, ACCORD, VADT as well as PRO-active (Kausik Ray *et al*, *Lancet* 2009; 373: 1765–72) would suggest that it is not correct to conclude that glucose control has no part to play to address CHD risk. They showed a significant 17% and 15% reductions in events of non-fatal myocardial infarction and coronary heart disease respectively with better control of blood sugar (mean HbA1c 0.9% lower in intensive arm). There was no impact on stroke or all-cause mortality. Of interest, ACCORD and PROactive as subgroups showed increase in heart failure (due to fluid retention) but this is not seen in all groups reflecting the glucose-lowering drugs used in these two trials. Overall, there is also a trend of higher non-CHD CV death in the intensive group, which could reflect arrhythmias. However, the UKPDS 10 year follow-up of patients who were given intensive glucose control (achieving HbA1c ~7.0%), suggest that initial intensive therapy followed by reasonable glycaemic control lead to clear macrovascular benefits not seen in the initial study period. They showed that despite early loss of glycaemic differences (after two years) between intensive and conventional groups, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarctions and deaths from any cause were observed during 10 years of post-trial follow-up. This would suggest that benefit from intensive glucose control on CVD takes a longer duration to manifest. To get CVD benefit hyperglycaemia must be controlled early after diagnosis and continued over a long term. As highlighted by the authors, an HbA1c goal of 7.0% for most patients seems reasonable and safe. This goal can be adjusted

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to < 6.5% for younger patients with no CHD and no risk associated with hypoglycaemia, and less tight control in those in whom CVD risk was higher. As mentioned by the authors, therapies directed at multiple related conditions such as dyslipidaemia, hypertension, hypercoagulable state, obesity, IR have to be undertaken. The Steno-2 showed that in type 2 DM, intensive intervention with multiple drug combinations and behaviour modifications had sustained effect with respect to vascular complications and rates of death including that due to CVD

Zul Hilmi pointed out that the criteria for selecting heart failure patients in whom cardiac resynchronisation therapy (CRT) should be looked at again (2). Using broad QRS duration alone to indicate presence of ventricular dyssynchrony can miss detecting patients suitable for CRT depriving them of this useful therapy. He suggests that measurements (SD of time to peak systolic velocity in 12 segments, Ts-SD-12) using the Tissue Doppler Imaging be used, being a superior criterion to predict response to CRT. He found that in patients with significant dyssynchrony, there was no significant correlation between QRS duration and the Ts-SD-12.

The treatment of hyperthyroidism (Graves' disease mainly) has changed little over 60 years with thioureylenes—carbimazole, methimazole and propylthiouracil, radioactive iodine therapy and surgery being the mainstay. The thioureylenes reduce thyroid hormones and favour immunological remission via direct or indirect effects. However, long term remission only occurs in 40-50% of cases, and many patients will need the other mentioned modalities. Vijay has described a case of aplastic anaemia more commonly associated with perchlorate (3). On the whole, agranulocytosis is rare (0.1–0.4%) and aplastic anaemia is very rare. It is important to note the potential for cross reactivity between CMZ and PTU. In Graves' disease the use of immunomodulation seems a logical therapy. Systemic steroids are not used except in severe eye disease, but there is a recent study from China looking at impact of intrathyroid dexamethasone on remission rates (XM Mao *et al*, *J Clin Endocrinol Metab* 2009; 94: 4984–4991). The use of rituximab has not caught on with few studies showing benefit.

Nazatul has demonstrated challenges encountered by breastfeeding mothers in a preliminary qualitative research (4). She has identified several obstacles. Measures must be taken to improve knowledge on breastfeeding, increase support from health professionals, parents and siblings

and improve facilities to express milk and to breastfeed at the work place and public places. More hospitals should become Baby Friendly in the real sense. It would be useful for these measures to be put in motion and her study repeated to see whether the implementation is successful or not.

Marzida Mansor identified the need of providing effective postoperative analgesia to mothers following Caesarean Section as the freedom from pain must be achieved without sacrificing mobility and mental alertness (5). She studied regular oral NSAID drug, diclofenac against the usual parenteral pethidine, an opioid type drug, in a randomised manner. Once the effect of spinal anaesthesia is over, patients took twice daily diclofenac orally versus subcutaneous pethidine. It would appear that there is still a need for the subcutaneous pethidine on the first postoperative day but the NSAID drug is adequate on the second and third day. As expected the NSAID does not cause sedation and received high overall satisfaction scores. A policy for giving opioids should be relooked so that the use can be rational rather than continued as a routine when the less centrally suppressive therapy can be just as useful.

Mafeitzeral wrote about experience in commissioning a new operating theatre at The University of Malaya Medical Centre (UMMC) Trauma Centre (6). Problems encountered were not all anticipated, but could be solved. International standards needed to be followed though they could not be adhered to entirely. The experiences recounted should be useful for others who are commissioning an operating theatre.

Muhilan described the construction and validation of a translated Overactive Bladder Screener for assessing urinary tract (7). OAB v8 was translated into Bahasa Malaysia but like all translated document, it is important that the translated version remains valid, accurate and retains the sensitivity and specificity of the screening test. The translated version was done by conventional means with back translation and review by a panel of experts. When tested in two groups of patients in a pilot study, the questionnaire demonstrated good internal consistency for component items and overall score. It was able to detect diagnostic items in both symptomatic and asymptomatic patients. It is considered to be suitable for use. Continuous scrutiny of this new tool should be practised and results of a larger sample should be analysed. Further modification of the translated version may be required.

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DIABETES CONTROL – THE LEGACY OF A MEMORY

Vijay AP, Chan SP

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ABSTRACT:

Achieving and maintaining good glycaemic control remains an important goal in the management of this common and prevalent disorder. Recent evidence from important megatrials, ACCORD, ADVANCE, VADT, UKPDS-10 year follow-up as well as the STENO-2 follow-up study, have cleared doubts concerning the benefits of targeting good glycaemic control. For the first time, we have the reassurance that macrovascular benefits can be realised from good glycaemic control. The legacy effect of prior good glucose control from the UKPDS-10 year follow-up, reinforces the results seen from the DCCT-EDIC (for Type 1 diabetes). The Intervention Phase of the UKPDS revealed benefits for reduction of microvascular complications, while it was only at the end of the Post-Trial Monitoring Phase where significant improvements in both micro and macrovascular outcomes were seen.

The other three Trials assessing the effect of glycaemic control on cardiovascular outcomes, although largely negative for CV benefit, give valuable insight towards appropriate patient characteristics for which aggressive glucose control can and should be instituted. Individualising glycaemic targets, which has been the approach that many clinicians have been practising, has received new impetus albeit with clearer details.

Getting to glycaemic goal early in the course of T2DM and Doing to Safely (Avoiding hypoglycaemia) are the key ingredients to successful management. The legacy of the memory of initial good metabolic/glycaemic control is investment in good health with benefits of reductions in both micro and more importantly, macrovascular disease, years later.

Multifactorial interventions that include blood pressure, lipid lowering in addition to glucose control in these individuals with the Metabolic Syndrome result in more immediate beneficial additive effects on cardiovascular outcomes. (*JUMMEC 2009; 12(2): 47-56*)

KEYWORDS: *Cardiovascular disease, clinical trials, diabetic complications, disease duration, macrovascular complications, microvascular complications, risk of hypoglycaemia, Type 2 diabetes, Type 2 diabetes treatment*

Introduction

The challenge facing all clinicians managing people with Type 2 diabetes mellitus (T2DM) is whether achieving and maintaining good/ideal glycaemic control is worthwhile. These efforts were sorely tested when the Action To Control Cardiovascular Risk in Diabetes (ACCORD) Trial was terminated prematurely, in February 2008, after only 3.5 years due to excess sudden deaths in the intensively treated arm.

Intensive control of glucose to glycated haemoglobin (HbA1c) values below 6.5% has been proven to reduce diabetic microvascular complications (1). The issue of the benefit of intensifying glycaemic control for

reduction of macrovascular complications is now more clearly understood.

The past two years have indeed been eventful—with the reporting from large megatrials. These trials include the following: ACCORD (Action To Control Cardiovascular Risk in Diabetes) (2),

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ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) (3), VADT (Veterans Administration Diabetes Trial) (4) as well as the UK Prospective Diabetes Study (UKPDS) 10 year follow-up data (5). Results from these important trials have informed and changed clinical management of T2DM.

Legacy of a Memory

The belief in the memory effect of previous good glycaemic control resulting in long-term vascular (both micro and macrovascular) complication reduction was mooted as far back as 2002 from the interim 4 and 8 year results of the DCCT-EDIC (Epidemiology of Diabetes Interventions and Complications) follow-up study. Such was the case even when glycaemic control is no longer ‘ideal’ or different between intensive and

standard glucose control subjects. This belief was further strengthened by the 10 year observational results from the EDIC6 (Figure 1). These results stemmed from the follow-up of patients in the original DCCT trial of Type 1 diabetic patients. At the end of the intervention phase of the DCCT, the patients were observed for another 8 to 10 years during which there was no longer any difference in glycaemic control. It was found that those in the initial Intensive good control arm over the intervention phase continued to reap the benefits of a decreased rate of microvascular and macrovascular complications. Similar results for individuals with T2DM were not available until the reporting of the UKPDS-10 year, post-trial monitoring results in September 2008, which found essentially similar findings as the DCCT-EDIC (5). These findings showed that intensive glucose control over the first 10 years of the life of a person with

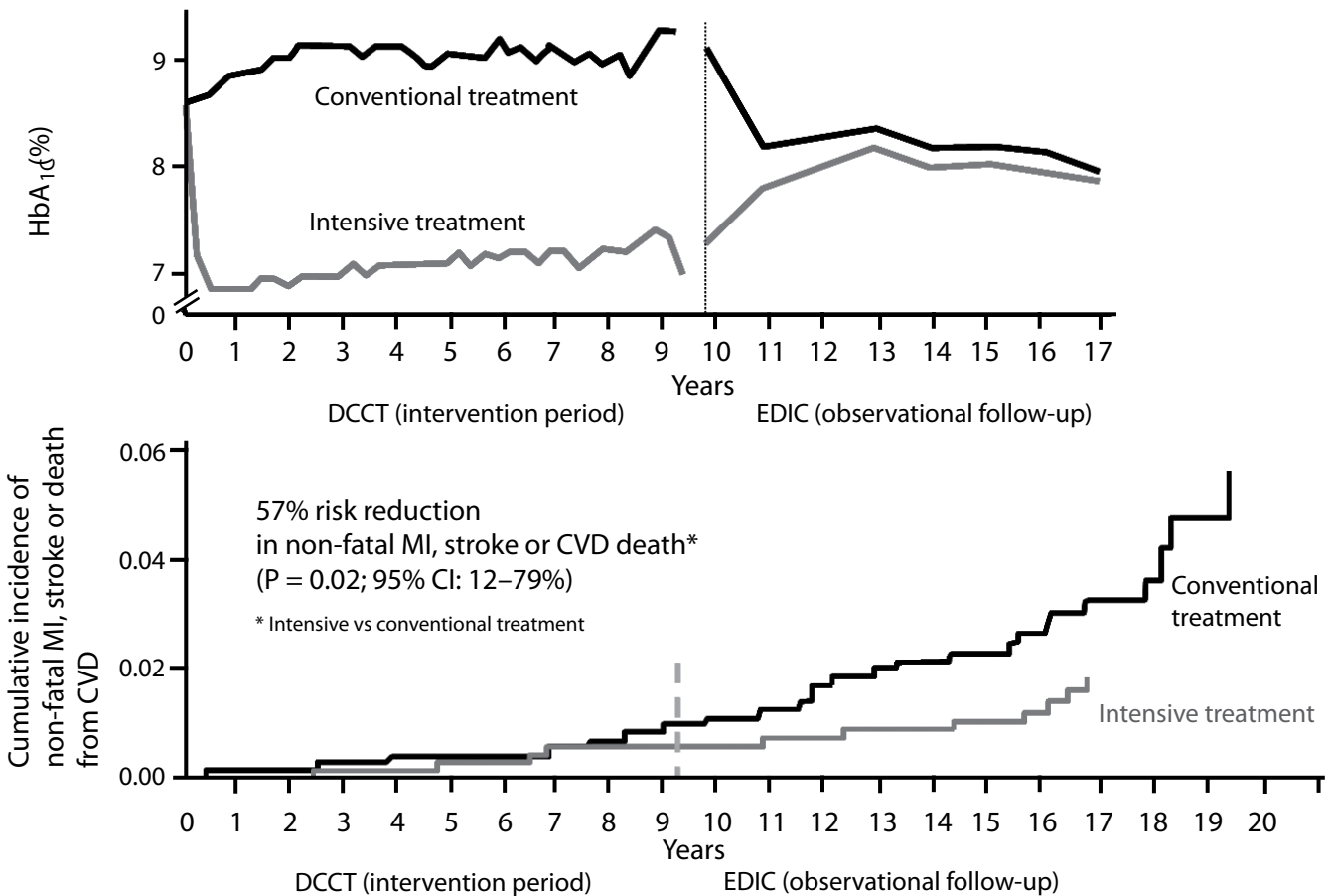
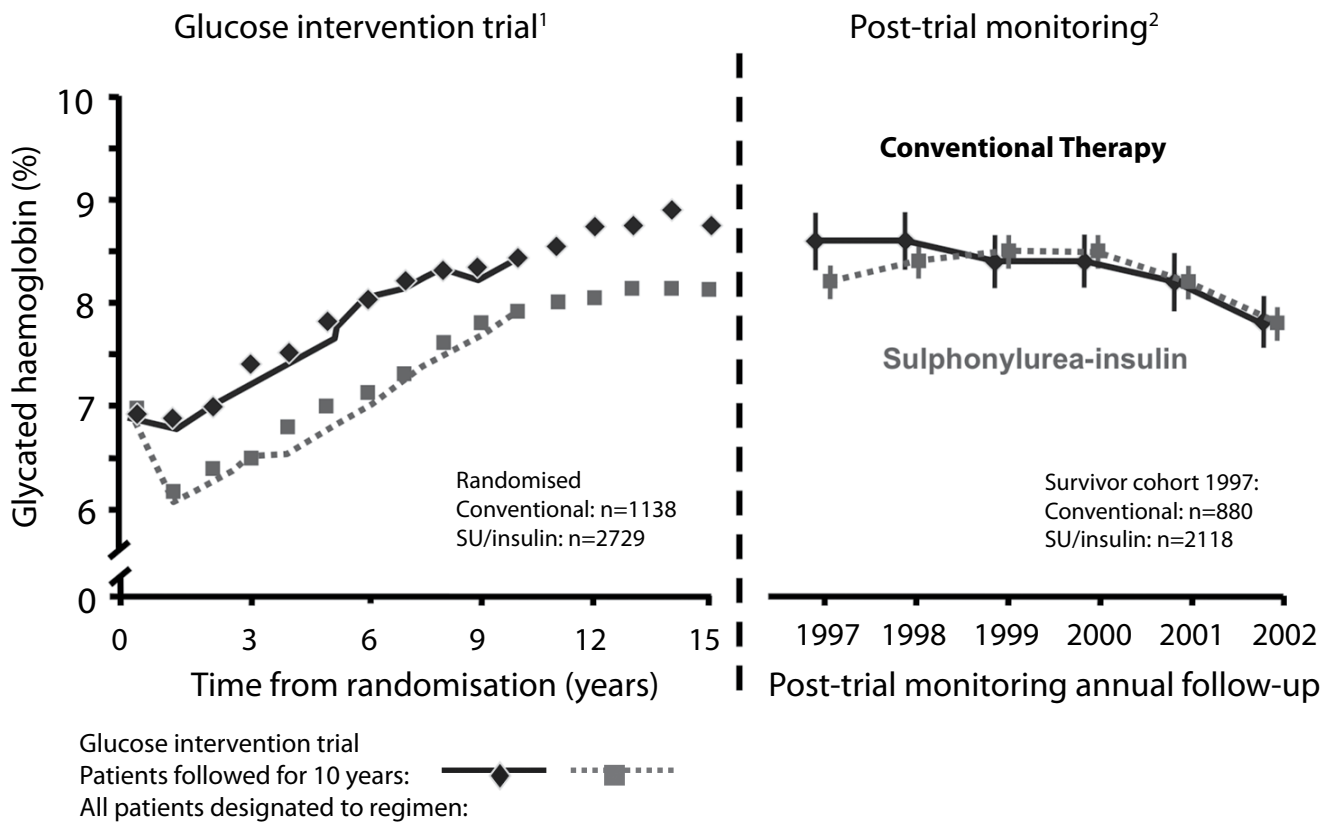


Figure 1: DCCT/EDIC (Type 1 diabetes mellitus): “Memory” of prior Intensive glucose control during the Intervention Phase results in significant reduction of Risk of CV disease during the EDIC (Observation Phase)
 Adapted from DCCT. *N Engl J Med* 1993; 329: 977–986. DCCT/EDIC. *JAMA* 2002; 287: 2563–2569. DCCT/EDIC. *N Engl J Med* 2005; 353: 2643–2653.



¹UKPDS Group. *Lancet* 1998; 352: 837–853.

²Holman R, et al. *N Engl J Med* 2008; 359: 1577–1589.

Figure 2: UKPDS post-trial follow-up: differences in HbA1c were not maintained after the Intervention Trial ceased

Table 1: UKPDS Post-Trial monitoring – Legacy Effect of Earlier Glucose Control

		End of Randomised Intervention ¹ 1997	End of 10-year observational follow-up ² 2007
Any diabetes related endpoint	RRR p-value	12% 0.029	9% 0.040
Microvascular Disease	RRR p-value	25% 0.0099	24% 0.001
Myocardial Infarction	RRR p-value	16% 0.052	15% 0.014
All cause Mortality	RRR p-value	6% 0.44	13% 0.007

¹UKPDS Group. *Lancet* 1998; 352: 837–853.

²Holman R, et al. *N Engl J Med* 2008; 359: 1577–1589.

Type 2 diabetes brought about in significant benefits, although glucose control was no longer different between previously intensive and standard treatment groups. This led to the coining of a new phrase “legacy effect” of intensive glycaemic control, by the UKPDS group, to leave their “footprint” in the field of diabetology (Figure 2 and Table 1) (1,5).

Further analysis from this landmark study (UKPDS) should therefore be noted. The subjects in the UKPDS were newly diagnosed, without significant cardiovascular complications, were younger (mean age 53 years) and had a lower baseline HbA1c at time of inclusion into the study. More importantly, the sub-analysis by Stratton *et al* (7), which reviewed the effect of updated HbA1c on micro and macrovascular complications. Without a threshold for improvement or reduction of these complications, it should continue to drive glycaemic targets (Figure 3).

People with Type 2 diabetes need to be informed that practising good glycaemic control for as long as possible is like investing in their bank for the possibility of a “lean” future—their investment will stand them in

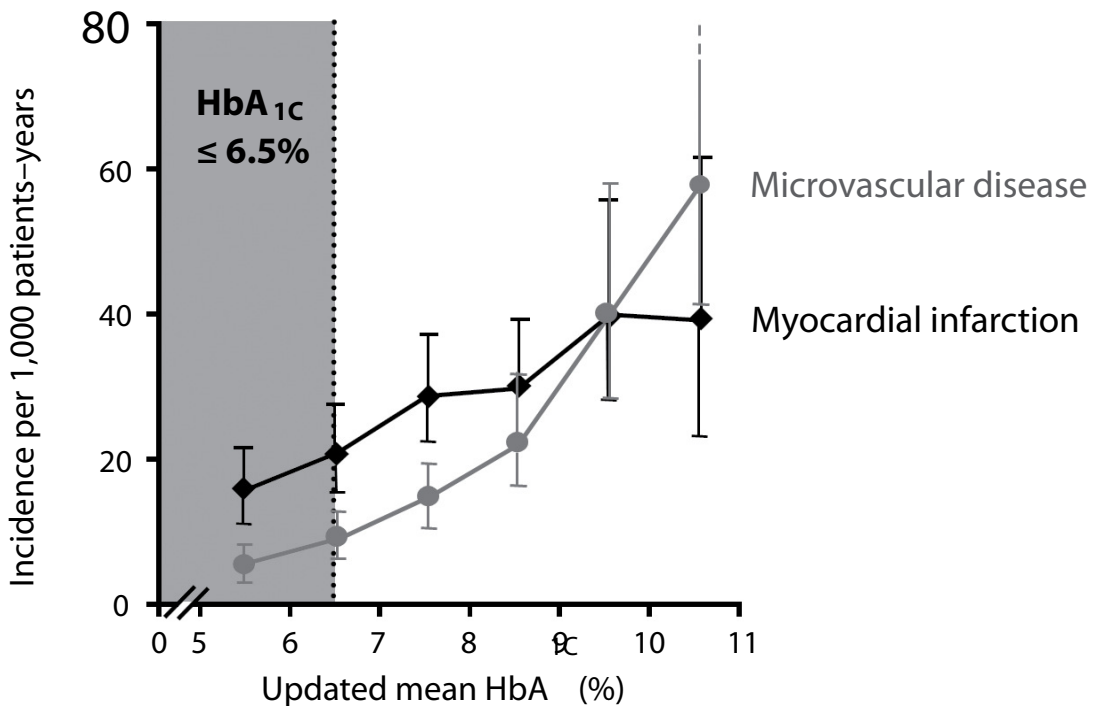
good stead when glucose control is more difficult and less ideal with persistence in lower risks of developing the dreaded diabetic vascular complications.

Thus, the legacy of the memory of prior good control is something that clinicians should continually remind themselves in their practice when managing the challenging task of achieving as well as maintaining good/ideal glycaemic control.

Glycaemic control — “Get ‘em Early”

When should good glycaemic control be achieved is the next key question that needs to be answered.

An observation from the UKPDS study population by S Colagiuri *et al* (8), noted that individuals with lower fasting plasma glucose at diagnosis and recruitment had fewer complications at baseline and fewer adverse clinical outcomes over the course of the trial. This was consistent with the belief that the earlier the detection and diagnosis in the course of T2DM coupled with appropriate glycaemic intervention, the better the outcome.



Study population: White, Asian Indian and Afro-Caribbean UKPDS patients (n = 4,585)
 Adjusted for age, sex and ethnic group Error bars = 95% CI

Figure 3: Incidence of myocardial infarction (MI) and clinical complications in type 2 diabetes is significantly associated with glycaemia. Adapted from Stratton IM, *et al*. *BMJ* 2000; 321: 405–412.

Analysis of the ACCORD study also confirmed that two subgroups did in fact benefit from intensive glucose control (2). The two subgroups comprised those with lower baseline HbA1c < 8.0% at recruitment as well as those without pre-existing cardiovascular disease.

Consistent with these findings, the VADT also showed that duration of diabetes had an impact on whether intensive glycaemic control produced cardiovascular (CV) benefits. Figure 4 shows that their data allowed them to develop an algorithm that suggested that CV benefit was found in those with diabetes duration of less than 15 years (9).

In fact, by the time the diagnosis of T2DM is made, we may have lost a lot of valuable time. Data from large epidemiological observational studies, such as the EPIC-Norfolk study, has noted that the relationship between HbA1c and cardiovascular disease and all-cause mortality is continuous—starting from HbA1c of 5.0% (10). This suggests that atherosclerotic vascular complications start well within the normal range of HbA1c, which is prior to recognition of diabetes.

Another well established fact is that individuals with glucose in the pre-diabetic range, i.e. impaired fasting glucose (6.1-6.9 mmol/L) and 2 hour post-OGTT 7.8-11.0 mmol/L) already have elevated risk of cardiovascular disease (CVD). Unfortunately, to date, there is no evidence that earlier interventions in individuals in the pre-diabetic phase will benefit with lower CV events .

Glycaemic Intervention – Negative CV benefit? Too little, Too Short (duration)...

To understand why the three recent CV outcome megatrials—i.e. ACCORD, ADVANCE and VADT—were negative, comparisons between patient characteristics entering these three trials and those of the UKPDS provide insights into the differences in outcomes. When these three trials are reviewed and juxtaposed to the UKPDS—it becomes retrospectively possible to understand that these trials were unlikely to show positive CV or macrovascular outcomes.

The UKPDS recruited newly diagnosed T2DM patients, who were younger, had less co-morbidities and

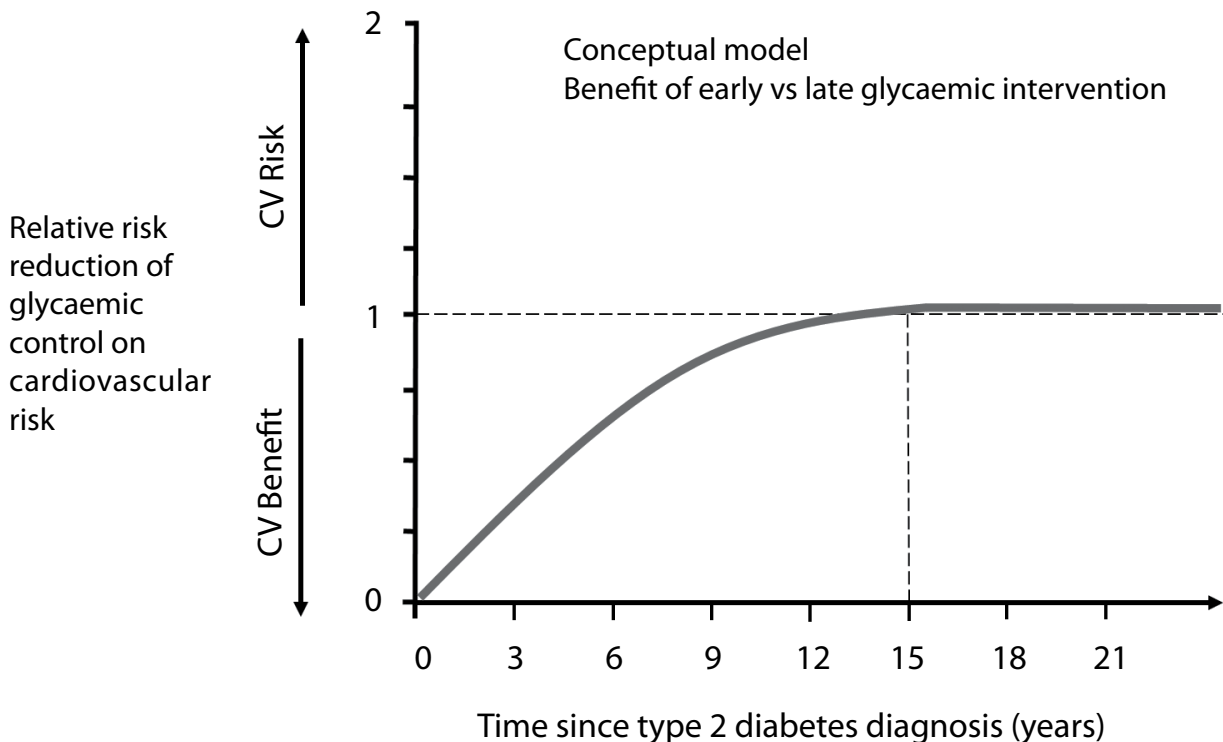
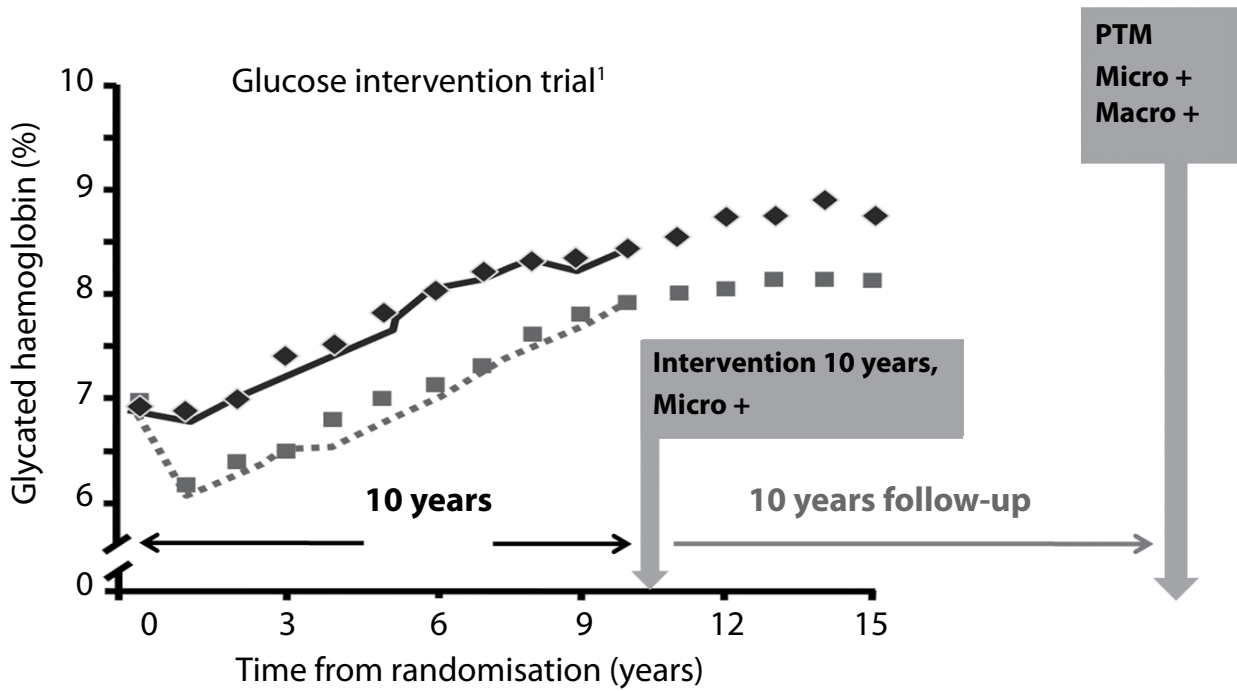
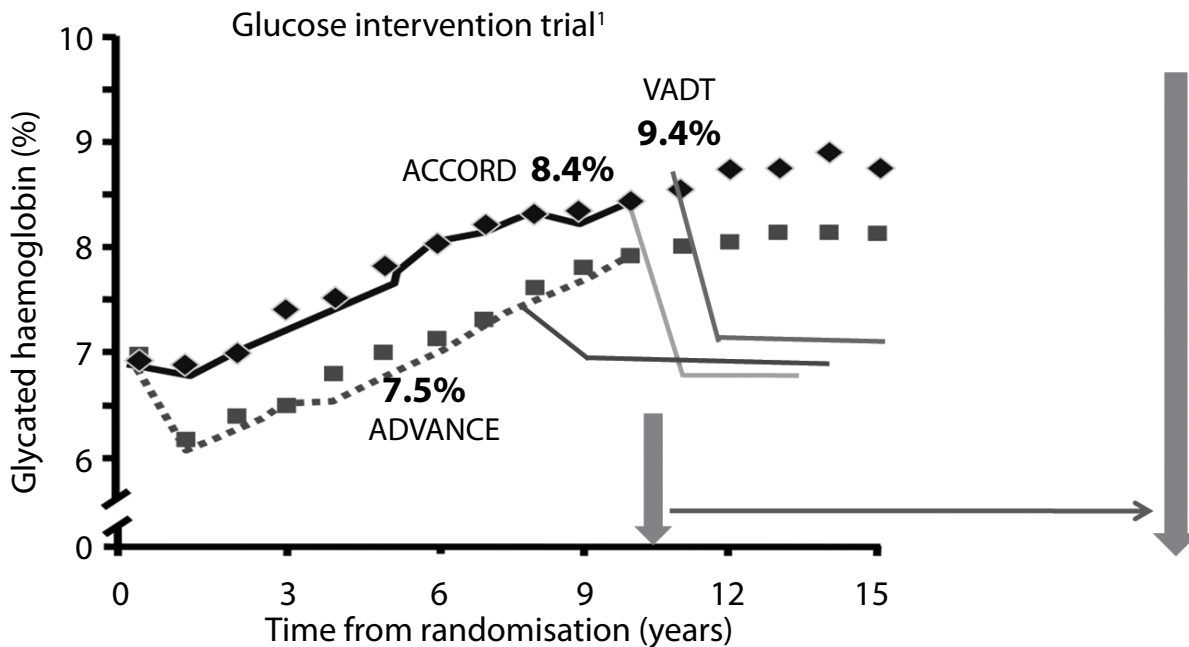


Figure 4: VADT - Relationship between time of intervention and the benefits of glycaemic control on macrovascular events. Adapted from VADT data presented at ADA June 2008.



¹UKPDS Group. Lancet 1998; 352: 837–853.

Figure 5a: UKPDS: Intervention Phase (10 years) followed by Post-trial monitoring (10 years)



LEGEND
 ADVANCE – baseline HbA_{1c} 7.5%, duration T2DM 8 years, duration 5 years
 ACCORD – baseline HbA_{1c} 8.3%, duration of T2DM 10 years, duration 3.5 years
 VADT – baseline HbA_{1c} 9.4%, duration of T2DM 11.5 years, duration 6 years

¹UKPDS Group. Lancet 1998; 352: 837–853.

Figure 5b: UKPDS with ACCORD, ADVANCE and VADT – Timelines of diabetes duration and differences in baseline HbA_{1c} at recruitment

lower baseline HbA1c. In Figure 5a, the UKPDS had a mean 10 year intervention phase followed by another 10 years of post-trial monitoring (PTM)—at which the macrovascular/CV benefit was eventually observed.

The three most recent trials recruited subjects who were older (60-66 years), had longer durations of diabetes (8-11.5 years), higher baseline HbA1c (7.5-9.4%) and a high proportion of people with established CVD (32-40%). In addition, Figure 5b shows that the duration of the interventions were short in comparison to the UKPDS, i.e. 3.5, 5 and 6 years respectively with no follow-up phase to observe CV benefits.

From Figure 5b, in retrospect, it is easy to understand that the three recent trials were unlikely to obtain positive CV outcomes by glucose intervention alone.

HbA1c, How Low to Go—“Fly in the Ointment”

Using the UKPDS data, 6.5% was determined by the International Diabetes Federation as the optimal therapeutic HbA1c target.

Unfortunately, the ACCORD trial data suggested that too aggressive glucose control was linked to the significant excess of sudden deaths. These deaths were largely presumed to be due to cardiovascular causes, in the Intensive arm (achieving HbA1c 6.4%) compared to their Standard arm (HbA1c 7.5%). Since then, there have been extensive and detailed discussions and reviews attempting to understand the reasons for this unanticipated increase in CV mortality. Due to these unfavourable results, the American Diabetic Association (ADA) recommended that the target HbA1c should be 7% (11).

Should all guidelines, therefore, adopt the ADA's recommendation? To answer that question, we are fortunate to have the results of the ADVANCE and VADT to help guide decision making.

The ADVANCE trial included a large proportion of Asian subjects—where Malaysia is proud to have been involved with the University Malaya Medical Centre (UMMC) being an investigational site. Results from this important trial are, therefore, relevant to the Asian region.

In the trial, similar patients to that of ACCORD and VADT were recruited. These patients were Type 2 diabetic individuals with very high CV risk, with up to 40% having established CVD at recruitment. Therefore, when the results were anticipated in June 2008, there was an air of disappointment as the trial was forecast to be negative with regard to its CV impact. The overall objective of tight glucose control was achieved in the Intensive arm of the trial, which was HbA1c 6.5% and the Standard arm achieved HbA1c 7.3%. Despite the lack of CV benefit when the final results of the ADVANCE trial were reported and published in June 2008, the overall outcome was still viewed in a positive light. To an extent, it counteracted the negative impact of the excess sudden deaths in ACCORD.

The negative cardiovascular ADVANCE and VADT results together took on a different significance in that they showed that it was possible to get to glycaemic targets of 6.5% and 6.9% respectively without causing excess CV mortality.

The question, then, is: What should be the optimal glycaemic target? For this, the UKPDS analysis of the impact of the updated HbA1c (Figure 3) on complications should continue to be used to inform decision making (3). As such, the need to achieve good glucose control in patients with T2DM early remains a key goal.

Glycaemic Control—“Do it Safely”. Avoid Hypoglycaemia

The debate surrounding the excess sudden deaths in the Intensive arm of the ACCORD continues. Although difficult to prove conclusively, the evidence points toward hypoglycaemia as one of the possible reasons for the sudden deaths. In a sub-analysis, it was recognised that individuals who had experienced any episode of hypoglycaemia had a higher CV mortality (12). Regardless of the intervention group, 2.9% Intensive arm and 4.9% of Standard arm suffered CV mortality in those who had experienced hypoglycaemia. In comparison, the mortality rate among individuals without hypoglycaemia were 1.3% in the Intensive arm and 1.0% in the Standard arm.

Results from the VADT also showed that recent severe hypoglycaemia was 4.0 times more likely to predict CV death in that population.

Other hypotheses that revolve around the excess CV mortality of the ACCORD suggest that too rapid reduction of HbA1c and excessive weight gain may also have been negative influences.

Multifactorial Interventions—“2-in-1” and “3-in-1” Trials

T2DM clusters in individuals who have other CV risks, namely the Metabolic Syndrome. These include hypertension, dyslipidaemia (low HDL-cholesterol and high triglyceride) and android obesity. It is therefore, not surprising that a multifactorial approach involving aggressive management of all these CV risk factors have been confirmed to confer immediate benefit on CV outcomes that was not seen with pure glucose control alone.

Multifactorial approaches that had a “2-in-1” therapeutic goal (glucose and blood pressure) in the UKPDS and ADVANCE showed significant reductions in CV outcomes (3, 13). The “3-in-1” approach adopted

by the STENO-2 (glucose + blood pressure + lipid lowering) had the best results with close to 53% reduction of CV mortality at the end of the eight year intervention phase (14). Figure 6 shows that after a further 5.5 years’ observation, during which glycaemic control was no longer different, persistence in benefit of a 50% reduction in CV mortality or all cause mortality continued to be seen (15). This is again evidence of the Legacy or memory effect of previous good metabolic control.

The expected question that arises from the results of these multifactorial interventions is whether improvements in blood pressure and lipid control contribute to the legacy/memory effect. The answer comes from the UKPDS-10 year post-trial monitoring results that revealed that with a loss of blood pressure difference in the BP arm of the study. There was no further protection seen on both micro as well as macrovascular outcomes (16). Therefore, with regard to blood pressure control and its beneficial effects on complications, “What you see is what you get!”.

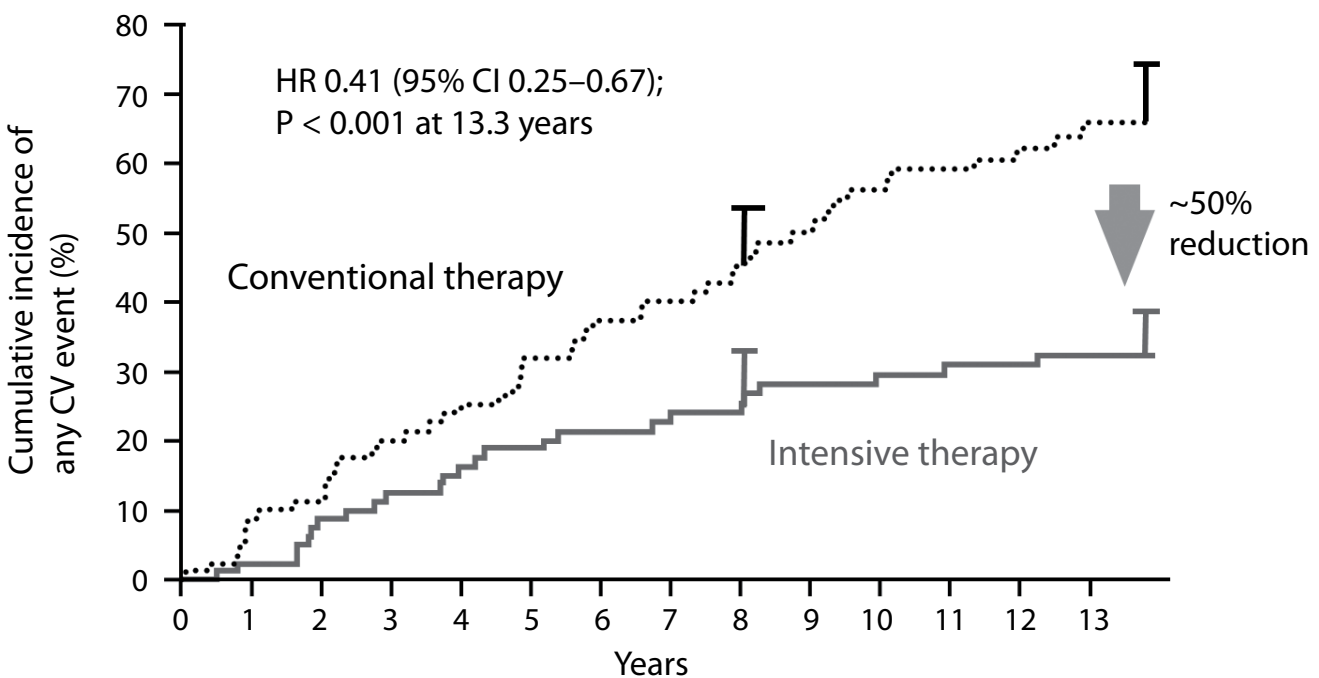


Figure 6: STENO 2: Multifactorial Intervention is Associated with Improved CV outcomes / Memory effect of prior Intervention shows persistence of benefit over another 5.5 years observation during which all parameters were no longer different^{14, 15}

Adapted from Gaede P, et al. N Engl J Med 2008; 358: 580–591.

Individualising Glycaemic Targets

From the large evidence base gathered using the recent megatrials, it is reassuring that what clinicians have been intuitively practising has been correct, which is to Individualise glycaemic goals.

Recent revisions in most guidelines, including the 4th Malaysian Clinical Practice Guideline for the Management of Type 2 diabetes 2009, reflect this with recommendations for glycaemic targets to be adopted according to each individual patient's circumstances—which are;

- To be aggressive, to achieve HbA1c <6.5%, in those early in the course of their diabetes, without comorbidities, with an expected long and normal life-expectancy
- To be more flexible and allow higher HbA1c levels in those with limited life-expectancy, history of severe hypoglycaemia, long duration of diabetes and comorbidities.

Conclusions

Macrovascular or CV benefits from good glycaemic control alone require many years of initial good control and then years—a decade more—before reaping the benefits of improved CV outcomes.

Multifactorial approaches involving aggressive management of blood pressure, lipid lowering. In addition to glycaemic control produces the CV benefits not seen with glucose control alone. Good blood pressure control does not have a legacy effect.

Given the evidence thus far, intensive glucose control remains an important and worthwhile goal—especially early in the course of the disease before complications (especially CVD) occur.

Glycaemic control—GET TO GOAL EARLY! GET TO GOAL SAFELY. Avoid hypoglycaemia!

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VENTRICULAR DYSSYNCHRONY IS COMMON AMONG HEART FAILURE PATIENTS WITH NARROW QRS COMPLEX

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ABSTRACT:

Current selection guideline for CRT uses broad QRS duration (>120 ms) as a marker for ventricular dyssynchrony. However, more recent data supports mechanical marker specifically measured by Tissue Doppler Imaging (TDI) as a better criterion to predict response to CRT. Sixty seven patients with significant left ventricular dysfunction (EF less than 40%) and narrow QRS complex were prospectively enrolled. They underwent Tissue Doppler Imaging (TDI) study to evaluate intraventricular mechanical dyssynchrony. Dyssynchrony index which is defined as standard deviation of time to peak systolic velocity in twelve ventricular segments was measured. A value greater than 32.6 is taken to reflect significant ventricular dyssynchrony. Overall 38 patients (56.7%) demonstrated significant dyssynchrony. There was no significant correlation between QRS duration and the Ts-SD-12 ($r = 0.14$, $p = 0.11$). Ventricular mechanical dyssynchrony is common in patients with normal QRS duration. Therefore, QRS duration alone will miss a substantial proportion of suitable patients for CRT and therefore deny them this adjunct therapy. We propose echocardiographic parameters, specifically TDI, to be included in patient selection criteria for CRT. (JUMMEC 2009; 12(2): 57-62)

KEYWORDS: oab, luts, validation, translation, questionnaire

Introduction

Cardiac Resynchronization Therapy (CRT) in the form of biventricular pacemaker has been shown to be an effective adjunct therapy in patients with drug-refractory heart failure and evidence of ventricular dyssynchrony (1-5). The current guidelines include broad QRS complex (greater than 120 milliseconds) as a marker for ventricular dyssynchrony (electrical dyssynchrony) (6). Nevertheless, emerging recent data support mechanical dyssynchrony as measured by Tissue Doppler Imaging (TDI) as a better predictor to CRT as compared to electrical dyssynchrony (7-11).

Aims

Our aims were to:

1. Determine the prevalence of ventricular dyssynchrony by using TDI among heart failure patients with narrow QRS complex.
2. Evaluate the correlation between QRS duration and ventricular dyssynchrony.

Methods

This study was approved by the University of Malaya Medical Centre research ethics committee.

Patients

The population consisted of 67 consecutive patients who were referred the echocardiography laboratory and who fulfilled the following criteria :

1. Age greater than 18 years old.
2. Left ventricular ejection fraction of less than 40%.
3. Narrow QRS complex as defined as less than 120 milliseconds.

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Patients with pacemaker or CRT were excluded from this study.

We did not include the functional class as one of the inclusion criteria because this was a study to specifically look at mechanical dyssynchrony as assessed by TDI. We felt functional class would be important if this were to assess the response of patients to CRT.

Echocardiography

Images were obtained with patients in the left lateral decubitus position using iE-33 (Phillips Medical System). Conventional 2-D M-Mode method was used to determine the ejection fraction, left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD). Aortic valve opening and closing time were measured from the apical 5-chamber view.

Tissue Doppler Imaging (TDI)

Tissue Doppler colour imaging was performed using 3.5-MHz transducer in apical long axis and apical 2- and 4-chamber views. Gain setting was adjusted accordingly to optimize colour saturation. Frame scanning rate of 100-140 Hz was used. At least three consecutive beats were stored and the images were digitalized and analyzed offline by using QLAB 5.0 (Phillips medical) software. Myocardial regional velocity curves were constructed from the digitalized images. The sampling was placed on the basal and middle segments of the septum and lateral walls (4-chamber view), inferior and anterolateral walls (2-chamber view) and posterior and anterior walls (apical long axis view). The beginning of QRS complex was taken as the reference point. The velocity curves from the three beats were averaged and the time to peak systolic velocity from the beginning of QRS complex was measured for each of the twelve segments. The standard deviations of the twelve segments peak velocities (Dyssynchrony index) were calculated and a value of greater than 32.6 ms was regarded as significant ventricular dyssynchrony.

ECG analysis

Standard 12-lead electrocardiograms were acquired at a paper speed of 25mm/second and a scale of 10 mm/mV. Prolonged QRS duration is defined as greater than 120 milliseconds.

Lead II was used to measure the QRS duration. Five QRS complexes were measured manually using standard ruler and the average value was taken as the final QRS duration.

Statistical analysis

Data were analyzed using statistical SPSS software (version 14.0, SPSS Inc., Chicago, Illinois). All parametric variables were compared using independent *t*-test. For comparison between more than two variables analysis of variance (ANOVA) was used. Pearson's correlation was used to examine the relationship of two continuous variables. Non-parametric variables were analyzed using Pearson's χ^2 test. A probability value of $p < 0.05$ (2-sided) was considered to be significant. The measurement of dyssynchrony index was performed by single investigator and the intraobserver variability was expressed as Pearson's correlation coefficient.

Results

Baseline characteristics are listed in Table I. The "uncertain" aetiology represented those patients who were newly diagnosed to have impaired left ventricular function and were still under investigation at the time of this study. We found 38 out of 67 (56.7%) patients had significant ventricular dyssynchrony. There was no significant correlation between QRS duration and dyssynchrony index ($r=0.09$ $p=0.47$) (Figure 1). The comparison of characteristics of patients and echocardiographic parameters between those with and without LV dyssynchrony is illustrated in Table II. The intraobserver correlations for 10 randomly selected patients for dyssynchrony index is 0.98 ($p < 0.001$).

Discussion

Different methods are currently being used to assess mechanical ventricular dyssynchrony (7-11). The dyssynchrony index, introduced by Yu (9), is thought to be the best method since it has shown excellent sensitivity and specificity in predicting response to CRT (10-11). The cut-off 32.6 millisecond is derived from the mean plus two standard deviation of the normal population in the study conducted by Yu and his colleagues (9).

The finding of the presence of ventricular dyssynchrony among heart failure patients with narrow QRS complex in this study is consistent with other studies around the world (9, 12-14). Unfortunately, these patients were excluded from CRT based on the current selection criteria.

The QRS complex represents the vectorial sum of electrical forces generated by myocardial masses over time. It is unable to convey the presence and severity of electrical delay in all ventricular segments and correlates particularly poorly with disturbance of distal conduction tissue. Furthermore, since QRS duration is only influenced by significant myocardial masses, regional changes represented by small vectors are inadequately displayed.

Interestingly, Auricchio *et al* documented heterogeneous left ventricular (LV) activation among heart failure patients with left bundle branch block morphology via LV endocardial mapping (15). Functional lines of block with different anatomic location within the LV were demonstrated and surface ECG recordings were unable to predict location and extent of ventricular conduction delays. This was compatible with tissue Doppler imaging (TDI) findings of variable location as well as extent of mechanical LV dyssynchrony that could not be predicted from QRS duration of a surface ECG.

In short, electrical dyssynchrony may well be linked to mechanical dyssynchrony but surface ECG is not sensitive enough to detect regional electrical delays as TDI does for regional mechanical delays. Secondly, some of these patients may have mechanical dyssynchrony without significant electrical delay in the presence of myocardial disease which does not involve the conduction pathway.

Moreover, Achilli *et al* demonstrated that clinical and functional benefit of CRT was similar in patients with wide or narrow QRS complex (16). It was the first study that included patients with mechanical dyssynchrony demonstrated by echocardiography but narrow QRS complex in looking for the benefit of CRT. Another more recent and larger study by Yu *et al* also showed CRT for heart failure patients with narrow QRS complex and coexisting mechanical dyssynchrony by TDI resulted in left ventricular reverse remodeling and improvement of clinical status (17). The extent of

the benefit was similar to that of wide QRS complex group.

We certainly need RCT to evaluate the response of the patients with narrow QRS complexes to CRT. Although studies so far have not shown favourable response to CRT for patients with narrow QRS complexes but those studies were small and from single centre trials. We need more evidence to illustrate convincingly ventricular dyssynchrony is common in patients with normal QRS duration. Ultimately, in order to change the practice, we need trials with large number of patients that include those with narrow QRS complex for CRT and show its benefits to them.

Table 1: Patient Characteristics and Echocardiographic Data (n = 67)

Variables	Value (n=%)
1. Gender	
Male	53 (79.1%)
Female	14 (20.9%)
2. Mean Age	59.1 (27.0-92.0)
3. Aetiology	
Ischaemic	37 (55.2%)
Non Ischaemic	11 (16.4%)
Uncertain	19 (28.4%)
4. Diabetes Mellitus	37 (55.2%)
5. Hypertension	40 (59.7%)
6. New York Heart Association Class	
li	33 (49.3%)
lii	31 (46.3%)
lv	3 (4.5%)
7. Medications	
Acei	49 (73.1%)
Beta-Blocker	29 (43.3%)
Digitalis	12 (17.9%)
Diuretics	44 (65.7%)
Statin	44 (65.7%)
Aspirin	52 (77.6%)
Anticoagulants	7 (10.4%)
8. Mean Lv Ejection Fraction (Ef) (Range)	25.4% (10.0-40.0%)
9. Mean Lv End Systolic Diameter (mm) (Range)	50.8 (30.0-78.0)
10. Mean Lv End Diastolic Diameter (mm) (Range)	59.1 (43.0-85.0)
11. Rhythm	
Sinus	61 (91.0%)
Atrial Fibrillation	6 (9.0%)
12. Mean Qrs Duration (Ms) (Range)	94.6 (74.0-117.0)

Table 2: Univariate analysis of lifestyle factors between cases and controls

Variables	Patients with LV dyssynchrony (n)	Patients without LV dyssynchrony (n)	p value
Gender			
Male	29	24	0.52
Female	9	5	
Age (mean ± SD)	58.2 ± 13.1	60.1 ± 12.8	0.55
Aetiology			
Ischaemic	18	19	0.29
Non-ischaemic	8	3	
Uncertain	12	7	
NYHA class			
II	22	11	0.21
III	14	17	
IV	2	1	
Diabetes Mellitus	19	18	0.32
Hypertension	23	17	0.88
Medications			
ACEI	28	21	0.91
B-blocker	18	11	0.44
Rhythm			
Sinus	36	25	0.23
Atrial Fibrillation	2	4	
Ejection Fraction (%) (mean ± SD)	26.1 ± 7.6	24.5 ± 7.6	0.39
LVESD (mm) (mean ± SD)	51.6 ± 11.0	49.6 ± 8.3	0.42
VEDD (mm) (mean ± SD)	60.0 ± 10.7	57.9 ± 7.1	0.36

Although several studies have consistently shown that TDI improves patient selection for CRT, the lack of uniformity of the method used to assess ventricular dyssynchrony limits its function at present. Different centers have their own method and technique to define ventricular dyssynchrony. Although the standard deviation of peak systolic velocity of twelve left ventricular segments (Dyssynchrony index) seems promising, but more data is needed to support its use as a standard method.

Our limitation is that, although the dyssynchrony index value of 32.6 is a reasonable value to be used in this

study since our local population are not very dissimilar in term of ethnic or geographical background to that in Yu's study, inclusion of normal controls to determine our own cut-off value and test its sensitivity and specificity for patient selection for CRT would be ideal. However, the number of our new CRT patients is relatively small; thus such study would take quite a long period to reach a reasonable target number of patients.

Conclusion

Ventricular dyssynchrony is common in heart failure patients with normal QRS duration. QRS duration

alone is not predictive of mechanical dyssynchrony as detected by TDI. Further studies especially large RCT's are needed to evaluate the response of heart failure patients with narrow QRS complexes to CRT. The selection criteria for cardiac resynchronization therapy may need to include echocardiographic parameters so that the benefit of this technology may be extended to a greater population.

Acknowledgement

The authors would like to acknowledge the support of the Cardiology Department at the University Malaya Medical Centre and in particular Mrs Rubiah, Anita and Suja for their assistance with the echocardiography studies.

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A RANDOMIZED CONTROLLED STUDY COMPARING SUBCUTANEOUS PETHIDINE WITH ORAL DICLOFENAC FOR PAIN RELIEF AFTER CAESAREAN SECTION

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ABSTRACT:

It is important to provide effective postoperative analgesia following a Caesarean section because mothers wish to be pain-free, mobile and alert while caring for their babies. The role of regular oral diclofenac as postoperative analgesia was evaluated in a randomized controlled study and it was compared to the established method of parenteral pethidine. Forty healthy women scheduled for elective Caesarean section under spinal anaesthesia with 2-2.5 mg of heavy bupivacaine 0.5% were randomized to receive either 75 mg of oral diclofenac twice daily or 1 mg/kg of subcutaneous pethidine every 8 hourly. Efficacy of pain relief (visual analogue score), patients' satisfaction and side effects such as sedation, nausea and vomiting were recorded for three days. The demographic variables were similar in both groups. Pain relief was adequate and comparable in both groups with similar mean visual analogue score during the second and third day of the study period. However, on the first postoperative day, 60% of the diclofenac group population required rescue medication consisting of subcutaneous pethidine in order to achieve the same pain scores as those in the pethidine group who did not require any rescue medications. Women who received oral diclofenac reported lower sedation and higher overall satisfaction. The incidence of nausea and vomiting was similar in both groups. This concluded that although oral diclofenac 75mg twice daily may not be superior to the traditional method of subcutaneous pethidine for pain relief following Caesarean section, it can still be used alone as an alternative, as it has other benefits of a non-opioid analgesia. (*JUMMEC 2009; 12 (2): 63-69*)

KEYWORDS: *diclofenac, Caesarean section, pethidine, postoperative analgesia*

Introduction

Various modes of analgesia can be used to provide postoperative pain relief. However, mothers who have had a Caesarean section are different from other postoperative patients because of their need and desire to be mobile as soon as possible in order to minimize postoperative complications and to allow for the care of their newborn.

Parenteral administration of opioids, usually by the intramuscular or subcutaneous route, together with antiemetics has been used as the predominant method of pain relief following Caesarean section in most parts of the world. More recently, newer techniques have become available. These include intrathecal opioids, continuous epidural analgesia, patient-controlled analgesia and patient-controlled epidural analgesia (PCEA). Although these techniques have been shown to produce better pain relief, they can

have many adverse effects requiring close observation of the women. They are also often expensive, require trained personnel and special equipment or monitoring and may restrict women from free and safe access to their babies, thus interfering with good early mother-child interaction.

The University of Malaya Medical Centre (UMMC) is a large public hospital with limited resources and staff, who cater to a large number of patients. There is a high turnover of mothers in the lower income

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group who are often left with minimal nursing care, expected to recover expeditiously to care for their newborns within a few hours following the operation, and who need to get back to their normal lives at home as soon as possible. It is not feasible to provide the majority of these mothers with more sophisticated methods of pain relief following Caesarean section. Subcutaneous pethidine has been used as the standard method of pain relief in the postnatal wards. However, they can cause sedation, drowsiness, nausea and vomiting and may affect the mother's ability and desire to breastfeed.

Breastfeeding is now encouraged worldwide and UMMC is in the process of becoming a baby-friendly hospital with 100% of mothers breastfeeding in the postnatal wards. It is therefore becoming even more important that inadequate pain relief or excessive sedation, nausea and vomiting does not become a barrier to these breastfeeding mothers. It is our observation that most mothers prefer oral analgesia that does not cause any drowsiness, sedation or nausea and vomiting. They are often willing to put up with some mild discomfort in exchange for alertness and mobility in order to care for their newborn. A few studies have shown that oral medications such as paracetamol, aspirin, morphine and ibuprofen, either on its own or as a combination, can be used either individually or in combination to provide effective analgesic therapy for women following Caesarean section (1-3). However, none of these studies compared the oral analgesia to the traditional regimen of parenteral opioids. In this prospective, randomized control trial we aimed to evaluate the efficacy of oral diclofenac, 75 mg twice daily, as the postCaesarean analgesia and compare it to subcutaneous pethidine, 1 mg/kg, every 8 hourly.

Materials and Methods

This study was approved by the UMMC ethics committee. After written consent was obtained, the study was conducted on 40 healthy women with a single fetus scheduled for elective Caesarean section under spinal anaesthesia. Exclusion criteria included those aged under 18 years and with known contraindications to the use of non steroidal anti-inflammatory drugs (NSAIDs) such as hypersensitivity, renal impairment, bleeding disorders, gastric problems and asthmatics.

The women were randomized into two groups—Group P and Group D—of 20 patients each by the drawing of shuffled coded envelopes. All patients fasted overnight and received premedication with 150 mg of oral ranitidine the night before the operation, another 150 mg the morning of the operation, and 30 ml of sodium citrate on arrival to the operating theatre. All received 0.5% heavy bupivacaine 2-2.5 ml. No other analgesia was given intraoperatively. All were monitored with a standard ECG, non-invasive blood pressure monitor and oximeter. On the basis of usual departmental guidelines, 20 ml of plain bupivacaine 0.5% was infiltrated locally by the obstetrician and 50 mg of diclofenac suppository was administered rectally to all patients immediately after surgery, while still on the operating table.

Women in Group P received subcutaneous pethidine 1 mg/kg before they were discharged from the recovery room. They continued to receive 1 mg/kg of pethidine subcutaneously with 10 mg of metoclopramide intramuscularly every 8 hours in the postnatal ward for three days. Women in Group D received oral diclofenac sodium 75 mg twice daily. The first dose of the oral diclofenac was given on the evening of the operation day (Day 1 p.m.).

Each woman was made aware that a dose of pethidine (1 mg/kg subcutaneously 3 hourly PRN) was available on request should the existing regular pain regimen did not provide adequate pain relief. Patients indicated their Visual Analogue Score (VAS) for pain at rest, nausea and vomiting and patient satisfaction twice a day, in the morning and evening, from the first to the third evening of the operation (a total of five recordings per patient), prior to receiving the oral diclofenac or subcutaneous pethidine. VAS were assessed by measurement on a 100-mm visual analogue scale ranging from zero for "no pain" and "no nausea" to 100 for "the worst pain imaginable", and "severe, intractable vomiting". VAS for patient satisfaction was evaluated using the same scale but ranging from 100 for "very satisfactory" to zero for "not satisfactory at all".

Patients were asked to slide a mark along a scale that indicated the level of pain, nausea and vomiting and satisfaction. The level of sedation was evaluated once a day in the afternoon by the same independent observer who was blinded to the analgesia received, using a

scale of 0 to 3 (0: awake, 1: somnolent, but responsive to verbal stimuli, 2: responsive to touch, and 3: deeply asleep).

The total amount and number of times when pethidine was requested and given was recorded.

Using Atlman’s nomogram (4), it was estimated that a sample size of 40 patients would detect a 30% difference in the satisfaction score with 80% power and type I error of 0.05. Data analysis was performed with the Statistical Package for Social Sciences (SPSS) version 10.0 software. Data is presented as mean (SD) or median (25th, 75th percentile). VAS pain, nausea and vomiting, and satisfaction scores were analyzed using an analysis of variance (ANOVA) for repeated measurements and independent sample *t* test. The sedation score was analyzed using the Mann-Whitney U test. A *p* value of less than 0.05 was considered statistically significant.

Results

Forty patients were enrolled in the study: 20 in Group P and 20 in Group D. One patient from Group D was discharged on the third morning of the operation and did not complete the last section of the evaluation (Day 3 p.m.), but her other data was included in the analysis. Age, weight and parity were similar in the two

Table 1: Demographic Data.

	Group P	Group D	P Value
Age (years)	30.4 (4.4)	31.4 (5.6)	NS
Parity	20 (1.00 , 2.75)	2.5 (1.25, 3.75)	NS
Weight (kg)	68.6 (6.7)	68.2 (6.9)	NS

Values are means (SD)

NS: not significant

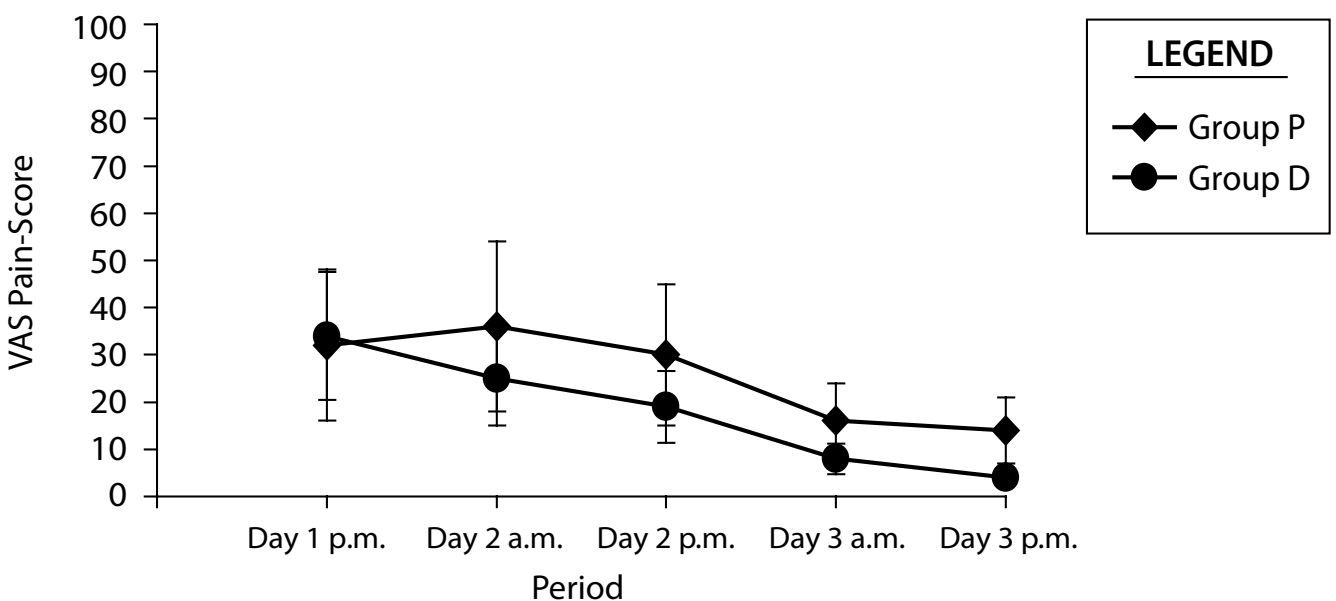
Table 2: Median Sedation Score (25th, 75th percentile) in Group P and Group D on 3 days Following Surgery.

	Group P	Group D	P Value
Day 1	2 (2, 2)	0 (0, 2)	0.000
Day 2	1 (1, 2)	0 (0, 0)	0.000
Day 3	0 (0, 1)	0 (0, 0)	0.024

by Mann-Whitney U test

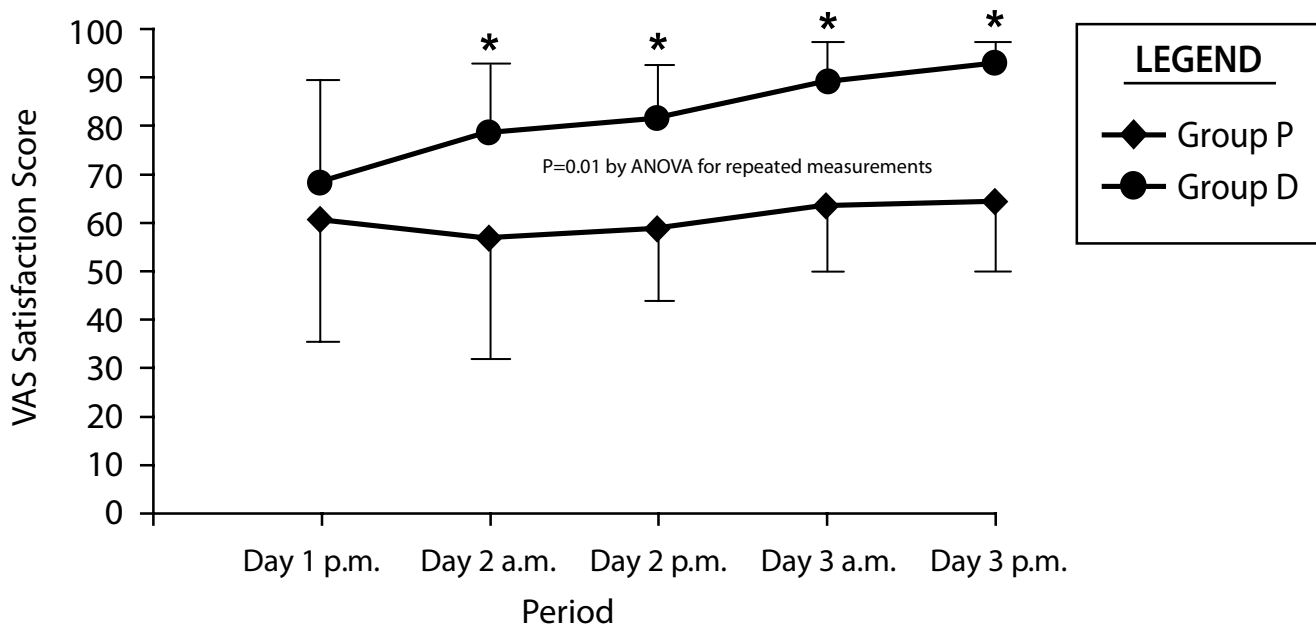
groups (Table 1). There was no significant difference between the two groups in the mean VAS pain score (Figure 1) and the mean VAS nausea and vomiting score for all three days following the Caesarean section.

Only two women in Group P reported mild nausea with a score of 10 and 25 respectively. Women in Group P were significantly more sedated than those in Group D (Table 2) on all three days following surgery. The satisfaction score was not significantly



Not significantly different by ANOVA for repeated measurements

Figure 1: Mean (SD) VAS pain score



* P < 0.01 by independent sample t test

Figure 2: Mean (SD) VAS satisfaction score

different in both groups on the first day but it became significantly higher in Group D on Day 2 and Day 3 of surgery (Figure 2). Twelve patients (60%) from Group P had refused one or more doses of subcutaneous pethidine. Twelve patients (60%) requested for rescue subcutaneous pethidine in Group D and none of the patients in Group P requested for any rescue medicine. Out of these twelve patients, nine requested for it once and three requested for it twice, all on Day 1 of surgery.

Discussion

Diclofenac is a benzene-acetic acid derivative that works like other NSAIDs by inhibiting the cyclooxygenase isoforms to mediate the body’s production of the prostaglandins implicated in pain and inflammation. A central anti-nociceptive effect has also been postulated (5-6). It has been widely used as part of the multimodal pain therapy for postsurgical analgesia. Several studies have shown that diclofenac suppository is opioid-sparing, reducing the opioid consumption between 35-40%, following Caesarean section (7-10). It has also been shown to reduce the PCEA requirement (11). Our study showed that while the sole use of oral diclofenac may not be adequate for analgesia on the first postoperative day when administered at regular interval, it may be used as the sole analgesia on the second and third day following Caesarean section.

Ideal pain treatment following Caesarean section should guarantee the mothers’ comfort, avoid side effects, allow for early ambulation and optimal interaction between the mother and her baby. Such a perfect technique of analgesia is not yet available. The traditional and most widely used method of parenteral opioids as well as the newer technologies such as patient-controlled analgesia, continuous epidural analgesia, patient-controlled epidural analgesia and intrathecal administration of various analgesics fall short of being the ideal pain treatment.

Oral analgesia is a relatively uncommon and underreported mode of postoperative pain therapy. Surgeons are reluctant to use oral analgesia immediately following abdominal surgery because of reduced gastrointestinal motility, decreased absorption of medications, nausea and vomiting and drowsiness from general anaesthesia. However, a Caesarean section is mainly done under regional anaesthesia and there is usually no handling of the intestine during the operation. Oral opioids have been used to treat post-Caesarean section pain, but, like parenteral opioids, it can cause excessive sedation (2,12). In a previous study, as many as twenty percent of the women treated with oral morphine chose to switch to another oral analgesic mainly because of complaints of sleepiness and drowsiness (2). On the contrary, our study and one previous study (3)

showed that oral non-narcotic drugs did not cause sedation while they provided adequate pain relief and high patient satisfaction when administered at fixed intervals.

In this study, the degree of pain was measured by using the 100-mm visual analog score. Work performed by Collins *et al* helped in the interpretation of VAS scores for pain (13). Their work suggests that patients with moderate pain (scored on a scale of none, slight, moderate, or severe) would score moderate pain on the VAS as >30mm (mean, 49 mm) and would score severe pain starting approximately 54 mm (mean, 75 mm). In our study, the VAS pain score was not significantly different in both groups. Most women experienced mild to moderate pain, implying that both diclofenac and pethidine provide equally good pain relief.

Neither oral diclofenac nor subcutaneous pethidine alone was likely to abolish post-Caesarean section pain totally. However, despite experiencing a similar level of pain, the women in the diclofenac group expressed higher overall satisfaction. Two factors may explain this finding:

1. these women were much less sedated than those in the pethidine group and thus felt more able to care for their newborns, which increased their level of satisfaction. This is reflected by the high number of women in the pethidine group (60%) who refused one or more doses of subcutaneous pethidine, citing drowsiness as unpleasant and undesirable, and
2. Diclofenac was shown to increase plasma concentration of endorphin and thus may improve patients' sense of well being (14).

Patient satisfaction is an essential component of quality of care. However, pain control may be only one of the variables affecting patient satisfaction. The levels of satisfaction with pain control did not correlate with the actual pain level. We believe that assessment of patient satisfaction should be used as a mode to monitor the quality of care in hospital settings rather than concentrating on measuring the pain level alone.

Sixty percent of the women in the diclofenac group requested for subcutaneous pethidine as rescue medicine on the first day of surgery, implying

somewhat inadequate pain relief with oral diclofenac alone. It is thought that pain after Caesarean section could be related to at least two components—a somatic one, which is the postoperative pain from the surgical wound; and a visceral one, due to uterine contraction. It is possible that the pain from the surgical wound was the predominant type of pain soon after the surgery and NSAIDs were less effective than opioids in relieving this somatic pain. This might explain the slightly lower satisfaction score on Day 1. By combining analgesic drugs with different modes of action, i.e. opioids with good effect on the somatic component and NSAIDs against the visceral pain, pain treatment after Caesarean section may become more efficacious.

Surprisingly, our study showed that mothers experiencing nausea and vomiting were not a significant finding in either group. This is contrary to the common belief that pethidine, an opioid, causes significant nausea and vomiting. Five factors may explain this finding. Firstly, the structure of pethidine is similar to atropine and local anaesthetics. Drugs with anticholinergic activity can reduce the incidence of nausea and vomiting. Also, the capacity of pethidine to produce nerve blockade could also contribute to a lower incidence of nausea and vomiting.

Secondly, pethidine was given via the subcutaneous route in our study. The maximal opioid plasma concentration could be lower with the subcutaneous route as compared to the intravenous group. Unlike the high "opioid peak level" produced by the intravenous route, the lower "opioid peak level" in the subcutaneous route might be insufficient to stimulate the chemoreceptor trigger zone, producing nausea and vomiting. Indeed a previous study has shown that patients in the pethidine group exhibited a lower incidence of nausea and vomiting than the patients in morphine group, and the incidence increased with increasing dose and with intravenous route (15).

Thirdly, we routinely gave metoclopramide together with pethidine, and this might have reduced the incidence of nausea and vomiting.

Fourthly, the reported incidence of nausea and vomiting may be lower in Asian women. Cepeda *et al* showed that black subjects had lower odds of nausea and vomiting than white subjects (15).

In humans, different races have distinctive pharmacokinetic and pharmacodynamic responses when exposed to medications or even cigarettes and alcohol. Existing knowledge about race differences in response to opioids is contradictory and requires further study.

Fifthly, the sample size of this study may be too small to detect the difference in the incidence and severity of nausea and vomiting between the two groups.

This study did not evaluate the effects of analgesia on the newborns in nursing mothers, but it is well known that morphine and other opioids enter breast milk rapidly with parallel concentration time curves for opioids in maternal plasma and breast milk. On the contrary, NSAIDs, being weak acids are not readily distributed to breast milk as they are readily ionized in the range of pH of breast milk. Therefore, they are not a concern for breastfeeding mothers. Neonates are affected negatively by opioids given to the mother (16). Depressed neurobehavioural scores due to accumulation of opioids and their major metabolites in colostrums and breast milk were found when opioids was given after partus using PCA technique (17). Such effects might also have negative impacts on the interaction between infant and mother as well as on the newborns' feeding behaviour during the first few days (18).

Our findings suggest that oral diclofenac is easily administered, is very cheap and provide satisfactory analgesia following Caesarean section with minimal side effects. It is superior to the traditional method of parenteral opioids. It is conceivable that newer techniques may provide more profound analgesia, this may be at the expense of increased side-effects, limitation of mobility and increased need for technology. Presumably this better analgesia provided by the more sophisticated technologies for postCaesarean pain treatment may offer even more satisfaction than oral diclofenac, but the expected small increase in satisfaction from a score which is already high makes the cost-effectiveness of these new technologies questionable.

Conclusion

In this study of elective Caesarean section under spinal anaesthesia, we found that the use of regular

oral diclofenac 75 mg twice daily may not provide comparable pain relief on the first post-operative day, but it provided superior patient satisfaction as compared to the traditional method of subcutaneous pethidine 1 mg/kg. Although offering less than perfect analgesia, oral diclofenac provided comfort to the patients with few side effects and can be monitored on the ward. The use of oral diclofenac 150 mg daily did not seem to have any significant side effects in this group of healthy parturient. Therefore, it is still acceptable to use diclofenac alone as an alternative pain relief following Caesarean section, in view of the other benefits of a non-opioid analgesics and especially in places where newer techniques are neither possible nor practical. However this is only a pilot study, a bigger sample size would be needed to confirm the findings.

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CHALLENGE AND SUPPORT FOR BREASTFEEDING IN HIGHLY MOTIVATED MALAYSIAN MOTHERS

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ABSTRACT:

The exclusive breastfeeding rate in Malaysia is very low. However in recent years the awareness of breastfeeding among mothers has increased. A preliminary qualitative research was carried out on these motivated mothers. The objective of this study was to understand the challenges encountered by breastfeeding mothers and to explore the support and motivation received by them. Information from the motivated mothers was obtained from focus group discussion. Some obstacles faced by the mothers were lack of knowledge on breastfeeding and lack of support from health professionals, parents and siblings. Facilities to express breast milk while at work were not readily available. The main motivation to breastfeed came from the mother herself and support from the husband. A holistic approach must be used to help mothers to continue breastfeeding. This includes breastfeeding promotion and education, setting up more Baby Friendly Hospitals, availability of breastfeeding support groups and provision of enough breastfeeding facilities at work and public places. (*JUMMEC 2009; 12 (2): 70-73*)

KEYWORDS: *breastfeeding, challenges, motivation, promotion, support group*

Introduction

Human lactation is the natural way to provide nutrition (1, 2) prevent childhood diseases (3, 4, 5) and to provide love and affection to the baby (6, 7). Not only does breastfeeding benefit the baby, it also protects the mother from certain diseases (8, 9, 10) and it is considered as a cost effective method of infant nutrition (11, 12). In addition, breastfeeding has always been the intended way of human survival.

Even though breastfeeding is the main method of infant nutrition, the exclusive breastfeeding (EBF) rate in Malaysia is very low. In a recent National Health and Morbidity Survey (NHMS III) held in 2006, only 14.5% of Malaysian mothers exclusively breastfed their babies up to 6-month old (13). On another note, the recent implementation of Baby Friendly Hospital Initiative has promoted the awareness of breastfeeding among mothers (14). We conducted a preliminary qualitative research on mothers who are highly motivated and who have decided to breastfeed their baby before the baby was born. The objective of this study was to understand the challenges faced by breastfeeding mothers and to explore the support and motivation received by these mothers.

Methodology

The age of mothers ranged from 26 to 35 years old. The majority of them were multiparous. Most of them were professionals with total household income of more than RM4,000.00 per month. The majority obtained tertiary education. The main challenge faced by these mothers was the lack of breastfeeding knowledge. Even though they were aware of the benefits of breastfeeding, and they had intentions to breastfeed their babies, they were not given or did not seek out for enough information about breastfeeding techniques. These were illustrated by the following example:

".. not much of an exposure. Did not ask from anybody. Did not look for any information. I breastfed him at night but during daytime (when I was at work) he was given formula milk." (I, 27, clerk)

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Most of these mothers faced the biggest challenge when they delivered their first child. The experience of handling a new born baby was overwhelming, let alone to breastfeed the baby. Several mothers also complained that they had some breastfeeding problems such as engorged breast, cracked nipple and inverted nipple. One mother said,

"First few days only a little bit of colostrum. By the third day the breast were engorged but nothing came out. My baby cried like mad. Very painful." (NS, 33, doctor)

These problems led to a stressful confinement period, as faced by some of the mothers. This was aggravated by the lack of support from their parents. In Malaysia, it is common for the parents or parents in law to take care of the new mother during the confinement. However, the strong belief held by the grandparents that formula milk is superior to breastmilk made the breastfeeding experience even more difficult as shown by these examples:

"...after that we stayed with my mother-in-law. If [it was] my own mother, we can say what we want. But if [it was] with my mother-in-law I couldn't say much. I didn't want to hurt her feelings. It was difficult to say... Furthermore my baby was their first grandson. During confinement, she used to take my baby and he slept in their room. They only gave him to me if he wanted to breastfeed..." (N, 26, technician).

"...I started to breastfeed the brother [from a pair of twins]. I had to remind a lot of people. They wanted to give formula milk, I said "No I want to breastfeed him first..." (F, 28, lecturer).

Apart from challenges in the home, mothers also encountered difficulties in hospitals. Some of the hospitals, especially in the private sector do not have a policy in place to support breastfeeding. In some cases, no permission were asked from these mothers when formula milk was fed to the baby during the admission period.

"I delivered my first child at a non baby friendly hospital. They did not ask whether I want to

breastfeed the child or not. Even the first day he was given a bottle of formula milk..." (A, 31, executive).

Some mothers had difficulty expressing their milk at the workplace. Problems such as no proper place to pump and non flexible working hours are the challenges faced by these mothers. Other issues that were discussed include postnatal blues, postnatal depression, breastfeeding discomfort, embarrassment, restricted freedom, insufficient milk, having a premature baby and having a pair of twins are part of the challenges in breastfeeding.

However, most of these mothers have succeeded in their mission to breastfeed their babies. The main motivation came from within themselves whereby they were determined to breastfeed their child. A mother mentioned,

"Starting from that [moment], when we went to the class we have decided... that whatever happened we wanted to breastfeed the baby. During the class the speaker had told us what would be the challenges... so we were told the expected problems beforehand..." (NK, 34, webmaster).

Apart from themselves, most of these highly motivated mothers were fully supported by their husbands.

"Surprising! When I was pregnant I wanted to breastfeed. We went to a shopping complex where a parenting expo was held. We were at the Medela booth. He said, 'This is a good brand.' He was more advanced! 'There is a website what, is it? Susuibu dot com?' He told me about the website. We bought the twin pump on the spot." (F, 28, lecturer).

"He will dismantle the breastpump apparatus, label all the bottles. Help like that is enough for me. He understands the breastfeeding process. When I wanted to breastfeed, he supports me." (I, 27, clerk).

"I was lucky that my husband supports me 100%" (ZH, 31, technician).

Another important support received by these mothers were from the mother-to-mother support group. Even

though no formal support group was mentioned, these mothers appreciated the help, information and moral support that they received from other breastfeeding mothers.

“..met with a relative who was a breastfeeding advocator. She told me about breastmilk expression. I had never imagined it before. Coincidentally, my sister-in-law gave birth just 5 days before me. We motivated each other. She also breastfed her child...” (NK, 34, webmaster).

“At the office, I saw a friend expressing her milk. She told me how to do it. Only then [did] I understand a bit. After that, I bought a breastpump even though I was not even pregnant yet! I was motivated to breastfeed. My husband was surprised!” (I, 27, clerk).

Other factors that motivated and supported these mothers were bonding, good breastfeeding information from the hospital, supportive healthcare staff, supportive colleagues and flexible work time.

Discussion

Research conducted to explore the hindrances and motivation of breastfeeding in mothers from developing countries like Malaysia is scanty. Mothers from the present qualitative study were purposely recruited from a breastfeeding support group and they were highly motivated to breastfeed their babies. The rationale to select these mothers was to assess their perspectives and experience in managing breastfeeding in a typical Malaysian community. If these motivated mothers encountered difficulties in breastfeeding, what more for those who lack such motivation to breastfeed.

Therefore, the input from these motivated mothers are useful in looking at the breastfeeding problem, as a first step in exploring the root cause of non-motivation at the national level. Results showed that even though determination and motivation are important factors for successful breastfeeding, the mothers were not excluded from facing many challenges. The main challenges include inadequate breastfeeding knowledge, being a first time mother, breast and breastfeeding problems and lack of support from various parties.

Conclusion

A holistic approach must be used to help mothers to continue breastfeeding. This includes breastfeeding promotion and education to mothers and their immediate family members, setting up more Baby Friendly Hospitals covering the private hospitals, availability of breastfeeding support groups and provision of enough breastfeeding facilities at work and public places.

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CONSTRUCTION AND VALIDATION OF A MALAY VERSION OF THE OVERACTIVE BLADDER SCREENER FOR ASSESSING URINARY TRACT SYMPTOMS IN A MALAYSIAN POPULATION

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ABSTRACT:

The aim of this study was to validate the translation of the Overactive Bladder (OAB) Screener (OAB V8) to the Malay language. It was to assess the reliability of the screener in the context of a Malaysian population. The original screener consists of eight symptoms indicative of OAB that has been proven to be highly sensitive and reliable. Translation was done with a modification of the Brislin Method using back translation and a panel of experts as a final review panel. The pilot study had two groups; a symptomatic (n=19 patients) and an asymptomatic group (n=18 patients). All patients performed the test twice at two week intervals once at the clinic and subsequently at home. Test-retest method was used for reliability and Cronbach's alpha for internal consistency. The translated questionnaire demonstrated good internal consistency in both groups of patients for all eight items individually and for the total score. Cronbach's alphas ranged from 0.972 to 0.981 for the symptomatic group and from 0.750 to 0.976 for the asymptomatic group. Test-retest correlation for all items was highly significant. Intraclass correlation (ICC) was high for both the asymptomatic (ICC ranging from 0.600 to 0.953) and the symptomatic group (ranging from 0.944 to 0.989). The Malay OAB V8 showed itself to be suitable for use, reliable in distinguishing symptomatic and asymptomatic patients and a valid instrument. (*JUMMEC 2009; 12(2): 74-82*)

KEYWORDS: OAB, LUTS, validation, translation, questionnaire

Introduction

Overactive Bladder (OAB) is a disorder affecting 10% to 20% of almost all surveyed population. It is characterized by urinary frequency, nocturia, urgency and urinary incontinence. Its primary impact is on the quality of life of those affected and their caretakers (1).

OAB is very common with a prevalence of about 17% in the United States (2) and 6–35% in Europe (3). The overall prevalence of OAB symptoms in individuals aged more than 40 years was 16.6%. The prevalence of OAB symptoms increases with advancing age. Frequency (85%) was the most common reported symptom, followed by urgency (54%) and urge incontinence (36%).

The prevalence figures for OAB in South East Asia population are available from a small study done in Singapore (4), and the 1998 questionnaire based survey to study the prevalence of urinary incontinence in Asia conducted by the Asia Pacific Continence Advisory Board (APCAB) (5).

The APCAB survey involved 7875 patients attending hospital for non-urological or non-gynecological reasons (4, 5). Eleven countries participated in the study including China, India, Indonesia, Malaysia, Singapore, Thailand, Philippines and Taiwan. A questionnaire-based survey was performed in 5502 females (5), and 2369 men from participating countries (4). The overall prevalence from the first APCAB study was 53.1% (5) with only 21.1% seeking treatment (4). From the second male population study, the prevalence was 29.9% out of whom only 5.9% obtained treatment. Both the APCAB studies demonstrated that very few patients had sought treatment for their OAB.

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Similar figures were seen in three other separate studies from Taiwan (6) and Malaysia (7, 8). In Taiwan OAB had a prevalence rate of 16.9%, with only 13% seeking treatment. In Malaysia, the prevalence was 19% in the female population (7) and over 6% in males over 40 years of age (8). From the 19% surveyed only 23.1% sought treatment since the majority (76.9%) did not see OAB as a problem to be treated (7).

These studies demonstrated that OAB is a problem in Asia and the majority of those suffering are not under any active treatment. Many did not seek treatment either due to ignorance about the disease or the treatment options that are available.

Therefore, there is considerable scope for improvement in terms of patient awareness and understanding of OAB. An objective OAB questionnaire/screener would be useful as its answers are in essence a patient's perception of their own disease and their evaluation of the symptoms that bother them. Currently, there are no reliable objective questionnaires for screening, evaluating symptoms or for measuring outcome (of OAB) in Malaysia—at least none that can be comprehended and used by the majority of the population. Both patients and primary care physicians would benefit from educational efforts to increase awareness of OAB. A questionnaire/screener in the local language would be a step in the right direction.

Methods

Study design

This study was conducted in two phases. The first phase was aimed at producing a cross culturally equivalent questionnaire (Figure 1). While, the second phase was focused on determining the measurement properties of the Malay questionnaire. We selected the OAB V8 (8-Item Symptom Bother Scale) based on its reliability and the reliability of its derivation from the OAB-q questionnaire (9, 10, 11). It is the most widely used and translated OAB questionnaire currently in use worldwide (12). A previous study had validated the psychometric properties of the OAB V8 (9).

In the first phase, the first step of the translation process was to obtain a basic Malay version for the foundation of the questionnaire. We used the Brislin

method for translating the English questionnaire into the Malay version (13). This process is similar to the International Consultation in Incontinence Modular Questionnaire (ICIQ) protocol (14). A translator fluent in both the Malay and English language translated the English OAB V8 into Malay. Two other independent translators then back translated this Malay version into English. All the translators were bilingual and fluent in both English and Malay. They were also experienced in the art of translation; having done similar projects in the past. The first translator was provided with sufficient information concerning the purpose of the questionnaire and the underlying concept. This was to ensure the translation was valid in terms of both language and context. The next two translators were blinded to this information.

An independent committee to determine the conceptual equivalence of the Malay translation then assessed these three translations along with the original. This committee chaired by the principal investigator consisted of three doctors from the Department of Surgery, Universiti Malaya—all of whom had some background in urology and has a good command of both the Malay and English language. After detailed discussions, the committee then either accepted the items or sent it back to the translator with a list of recommendations and suggested corrections. This review process was repeated to produce a conceptually equivalent translation.

Once approved by the committee, an additional step, which was not part of the original Brislin Method, was added. This was done as we felt the additional step would improve the questionnaire from a contextual point of view. This step was the review by an Expert Committee after scrutiny by an independent translator. The Expert Committee was formed by two professors from a Social Science background and a Urology professor. They were all based in local Malaysian universities. This phase of the study was aimed at producing a cross culturally adapted Malay version with content and face validity equivalent to that of the original OAB V8.

For the second phase, we enrolled 19 symptomatic subjects and 18 subjects who did not suffer from Lower Urinary Tract Symptoms (LUTS). The subjects

Soalan di bawah mengenai sejauhakah anda terganggu dengan gejala pundi kencing . Ada sesetengah orang akan terganggu dengan gejala pundi kencing dan tidak menyedari bahawa terdapat rawatan untuk mengubati gejala (simptom) ini. Bulatkan nombor yang dapat menjelaskan tahap kekerapan gangguan gejala(simptom) ini. Jumlahkan nombor-nombor ini untuk mendapat skor keseluruhan dan rekodkan skor di dalam kotak yang disediakan di bawah.

Berapa kerapkah anda terganggu dengan gejala (simptom) di bawah:	Tidak sama sekali	Jarang	Kadang-kadang	Selalu	Hampir selalu	Sepanjang masa
1. Kekerapan membuang air kecil/ kencing pada waktu siang.	0	1	2	3	4	5
2. Perasaan terdesak untuk membuang kencing.	0	1	2	3	4	5
3. Keinginan yang kuat secara tiba-tiba untuk membuang kencing dengan sedikit tanda atau tanpa sebarang tanda.	0	1	2	3	4	5
4. Air kencing terkeluar (beberapa titik) tanpa disedari .	0	1	2	3	4	5
5. Membuang air kecil pada waktu malam.	0	1	2	3	4	5
6. Tidur anda terganggu kerana bangun untuk membuang air kecil.	0	1	2	3	4	5
7. Rasa hendak kencing yang tidak dapat dikawal.	0	1	2	3	4	5
8. Terkencing disebabkan oleh rasa hendak kencing yang kuat.	0	1	2	3	4	5

Sila tambahkan 2 poin untuk keseluruhan jumlah skor jika anda lelaki.

Lelaki/Perempuan

Nama :

Umur :

Masalah/peyakit lain :

Jumlahkan respons anda bagi soalan-soalan di atas.

Kembalikan soal selidik ini kepada doktor apabila anda menemuinya. Jika skor anda adalah 8 poin atau lebih, anda mungkin mempunyai pundi kencing yang sangat aktif. Terdapat rawatan yang efektif untuk keadaan ini. Anda mungkin ingin berbincang tentang masalah ini dengan Pegawai Perubatan.

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Figure 1: Overactive Bladder (OAB) Malay Version (based on OAB V8)

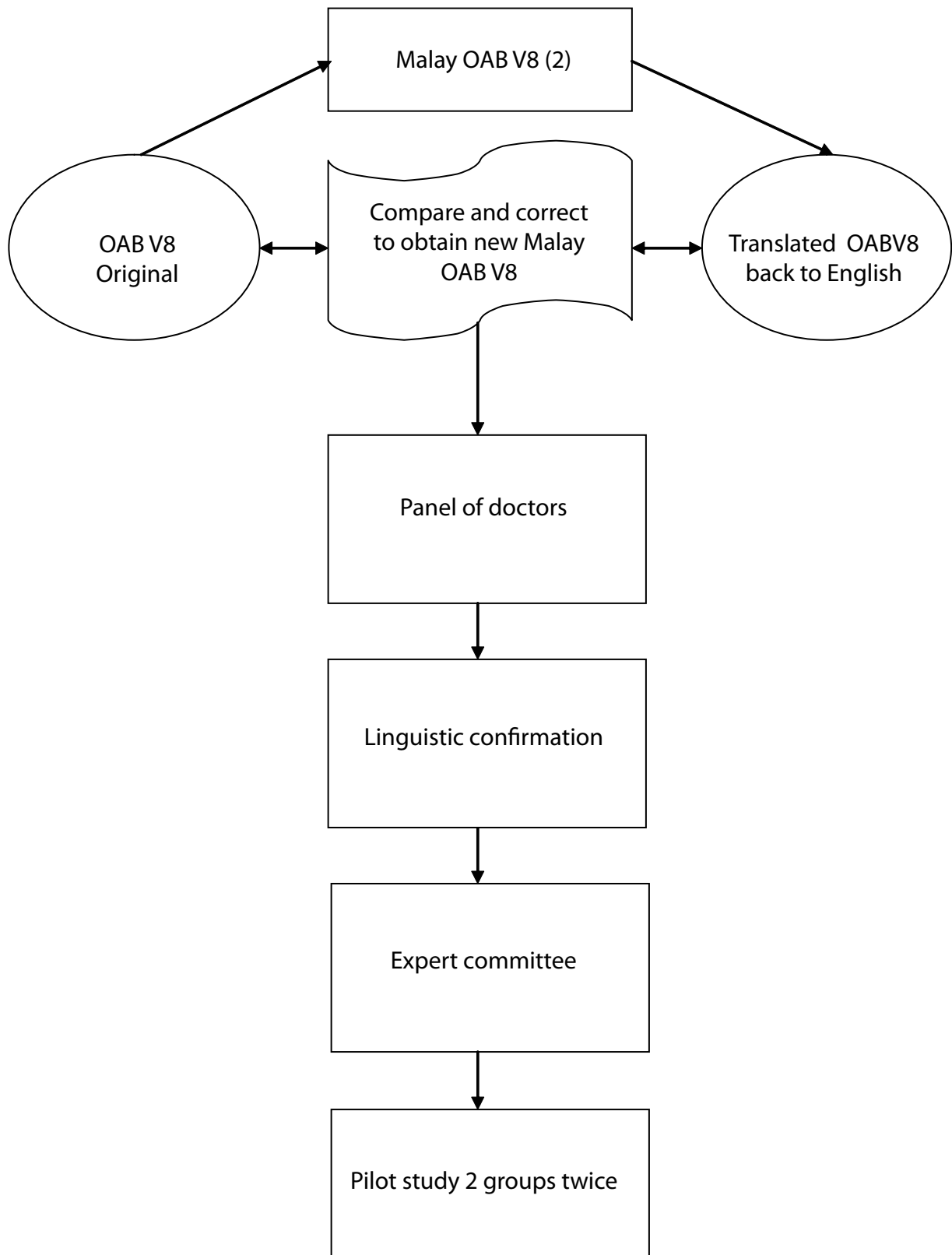


Figure 2: Overview of the cross cultural translation and adaptation of the OAB V8 from English to the Malay language.

were selected from the University Malaya Medical Centre (UMMC) based on the presence of their symptoms. None of these subjects had ever been exposed to a OAB or LUTS questionnaire in any language. Each subject completed the questionnaire on day one and was made to repeat the questionnaire after a two week interval. The second questionnaire was to be filled at home and mailed or handed back to the investigator at a later date. As all patients were on active follow up, all questionnaires were retrieved.

Statistical Analysis

All data obtained was entered and analyzed using the Statistical Package for Social Sciences (SPSS) version 13. Data included age, sex, and ethnicity, all eight items from the first test and subsequent retest. Normally distributed continuous variables were summarized as means \pm standard deviation (SD). The independent *T-test* was used to test differences between two independent means. Whereas, differences between two dependent means were tested using the paired *T-test*. When there were more than two independent means, the one-way analysis of variance (ANOVA) was used.

Their non-parametric equivalent tests were used when the distributions were not normal. Categorical variables are summarized as proportions and any differences were tested using the Fishers exact test. All hypothesis testing considered a two sided $p < 0.05$ to be statistically significant.

The psychometric properties of the Malay version of OAB V8 were calculated using the following:

1. Interclass correlation – Interclass correlation was used to assess the variation in total score among the different races. Wilcoxon/Mann–Whitney U test was further used to analyze the significance of the mean age difference between the groups.
2. Test-retest reliability – This was assessed using the intraclass correlation (ICC) which was arrived at by using Analysis of Variance (ANOVA). All eight points of the questionnaire were subjected to this testing with both groups being analyzed separately. Paired *T-test* was used to further assess the test-retest reliability

3. Scale Reliability – Cronbach's alpha coefficient was used to measure the internal consistency of the domains and the total score.

4. Discriminant validity – Independent *T-test* was to test for differences between the two groups as a measure of discriminant validity using Levene's Test for Equality of Variances.

5. Diagnostic performance – This was evaluated using the area under the Receiver Operating Characteristic (ROC) curve.

Results

Study Population

This study enrolled a total of 37 subjects. Of the 19 symptomatic subjects, 13 (68.4%) were females whereas 11 (61.1%) of the 18 asymptomatic subjects were females ($p=0.74$). The distribution of age among the subjects violated parametric assumptions, thus medians and the Mann Whitney U test was used. The median age of the symptomatic group did not significantly differ from the asymptomatic group ($p=0.26$). All the three major races in Malaysia—Malay, Chinese and Indian—were represented in both groups. In the symptomatic group Malays (57.9%) were the majority followed by the Indians (26.3%) and Chinese (15.8%). This was not statistically different from the asymptomatic group that was made up of 66.7% Malays, 22.2% Indians and 11.1% Chinese ($p=1.00$).

Interclass correlation

Interclass correlation was used to assess for variation in the scores between the different races. The results showed no significant difference between the various ethnic groups in terms of their total score ($p=0.737$). Hence, the conclusion was that the members of the various races answered with the same degree of reliability.

Discriminant validity

Furthermore, using the independent *T-test* we tested for the questionnaire's discriminant validity. The null hypothesis was that there were no difference in the scores between the symptomatic group and asymptomatic group. The mean score of 27.20 ± 2.19

Table 1: Validity and reliability for symptomatic individuals

	ICC	Cronbach's Alpha	Paired Mean Difference	95% Confidence Interval		p value
				Lower	Upper	
Q1	0.963	0.981	0.16	- 0.02	0.34	0,083
Q2	0.981	0.990	0.10	- 0.05	0.26	0,331
Q3	0.963	0.979	0.10	- 0.12	0.33	0,163
Q4	0.974	0.986	0.10	- 0.12	0.33	0,331
Q5	0.944	0.971	0.10	- 0.05	0.26	0,163
Q6	0.952	0.975	0.05	- 0.14	0.25	0,578
Q7	0.951	0.972	0.32	0.04	0.60	0,030
Q8	0.971	0.985	- 0.05	- 0.25	0.14	0,578
Total	0.989	0.994	0.90	0.22	1.57	0,013

Table 2: Validity and reliability for asymptomatic individuals

	ICC	Cronbach's Alpha	Paired Mean Difference	95% Confidence Interval		p value
				Lower	Upper	
Q1	0.928	0.955	0.06	-0.06	0.17	0.331
Q2	0.804	0.892	0.00	-0.17	0.17	1.000
Q3	0.600	0.750	0.00	-0.17	0.17	1.000
Q4	0.721	0.830	0.11	-0.05	0.27	0.163
Q5	0.893	0.915	0.06	-0.15	0.26	0.579
Q6	0.837	0.908	0.06	-0.06	0.17	0.331
Q7	0.825	0.895	0.00	-0.17	0.17	1.000
Q8	0.931	0.948	0.06	-0.06	0.17	0.331
Total	0.953	0.976	0.33	0.04	0.63	0.029

for the symptomatic group was significantly higher as compared to the asymptomatic group (mean=10.61 \pm 0.46) with a $p < 0.0001$. This indicates the ability of the questionnaire to discriminate between symptomatic and asymptomatic patients.

Test-retest reliability

Reliability was performed separately for the two groups of subjects. Table 1 shows the scale reliability for the symptomatic group. The Cronbach's

alphas for the symptomatic group ranged from 0.972 to 0.981 for the symptom bother score. This was associated with an Intraclass correlation coefficient (ICC) ranging from 0.944 to 0.989. This demonstrates high internal consistency. There was a significant difference in the paired scores of item 7 (mean difference of 0.32, 95% CI 0.04, 0.60) and in the total scores (mean difference of 0.89, 95% CI 0.22, 1.57). Though statistically significant, the differences were not clinically significant, and such variations are unlikely to affect the outcome of the screener.

Scale Reliability

Table 2 shows in the group of asymptomatic patients, the questionnaire showed more variability. The asymptomatic group's score while not as high as the symptomatic group is still acceptable with a Cronbach's alphas from 0.750 to 0.976 for the symptom bother score. This was associated with an ICC ranging from 0.600 to 0.953. This indicates that this group also has a high level of internal consistency and reliability. The ICC was lowest for items 3 and 4. For items 3, the correlation was 0.600 with a non-significant mean paired difference of 0.00 (95% CI -0.3171, 0.171). For item 4 the correlation was 0.721 with a non-significant mean paired difference of 0.11 (95% CI -0.50, 0.272). Interestingly, the total scores of the screener showed very good reliability with a score of 0.953 and had a significant mean difference between the test and retest of 0.333 (95% CI 0.038, 0.629). However, it is unlikely that this small difference will affect the interpretation of this screener.

ROC Curve

As expected the diagnostic performance of the questionnaire in this study comparing the symptomatic and asymptomatic subjects was very good. The area under the Receiver Operating Curve (ROC) was very high at 0.988. For screening, an optimum screening score of >12 gave a sensitivity of 94.7% with a specificity of 83.4%.

Discussion

The Brisilin method of translation is currently the most widely used method of translation. Most of the other language translations of the OAB V8 also utilized this method. Due to the format used, the process of translation, back translation and so on, there are numerous check and balances to identify and correct mistakes either from a linguistic or contextual point of view. Additionally, it is the current standards to which urology questionnaire translations are performed as set out by the ICIQ protocol. The limitation of this method is that it is manpower intensive as it requires two independent teams of translators and an expert committee who all need to work together.

In general, it should be easy to translate a sentence from English to Malay as the written language uses

the same alphabet and a number of Malay words are derived from English. The problem arises in that words that are directly derived may not be understood. Also contrary to popular belief Malay is not a homogenous language and there is variation from region to region. Further problems arose from the fact many disease symptoms do not translate well into the Malay language and require contextual rather than linguistic translation to make it accurate for example Urgency, urge incontinence or even incontinence. The concept of incontinence and urgency do not exist per se and need to be explained out. This can be a major problem in a questionnaire requiring self administration by the subject/patient.

For certain words it was difficult to translate using terms that were not considered rude. Hence in some parts two words with the same meaning were used to explain this e.g. "membuang air kecil" and "kencing" for micturation. In trying to overcome this problem it was decided to emphasize the meaning or the concept behind the question, rather than literary accuracy. In view of the above problems we decided to invite Bi-lingual social scientist and urologist to form an expert committee to evaluate the context of the question and make it more understandable and acceptable to Malaysians regardless of their background. This step is a deviation from current ICIQ protocols but a necessary one given the circumstances.

In the second phase of the study on the validation of data from the Malay OAB V8, it had performed as reliably as the original. It demonstrated great consistency in being to differentiate symptomatic and asymptomatic patients hence being able to act as a screener for OAB patients locally. The mean score of 27.20 ± 2.19 for the symptomatic group was significantly higher as compared to the asymptomatic group (mean= 10.61 ± 0.46) with a $p < 0.0001$.

Any bias from the presence of medical staff was eliminated by the fact that the questionnaire was self administered at home for a second time two weeks later and the subjects still answered with a great deal of consistency. Mean difference between the test and retest of 0.333 (95% CI 0.038 - 0.629).

The questionnaire demonstrated good internal consistency reliability, test-retest reliability,

discriminant validity. However, the high diagnostic performance (high specificity and sensitivity) (ROC is high at 0.988) should be viewed with caution. A screener is expected to be highly sensitive but not very specific, criteria met by the OAB V8 (sensitivity of 94.7% with a specificity of 83.4%). This is because the two groups were selected based on the presence of their symptoms. The symptomatic groups had gross OAB and the asymptomatic patients were healthy individuals. The wide variation in the symptoms may have influenced the study.

The data obtained is remarkable considering the difficulties encountered with the language and the unfamiliarity of many of the subjects with the use of written questionnaires as a form of data collection. However there was no control group for comparison i.e. those using the English OAB V8 for comparison in regards to use of a questionnaire.

A larger cross-sectional study should resolve any doubts about the sensitivity and specificity in relation to the ROC curve and comparison against subjects answering using the OAB V8 English should answer any questions on administration of a questionnaire.

The limitations encountered were in the selection of patients as a truly randomized population survey would not accurately reflect the population characteristics e.g. Malaysian population is predominantly Malay (65%) however the urban population served by the hospital (UMMC) has a larger percentage of Indian and Chinese patients.

Conclusion

The Malay OAB V8 showed itself to be suitable for use in the community. It was reliable in distinguishing symptomatic and asymptomatic patients and is a valid instrument for studies to be conducted in Malaysia.

Declaration: This study was done with a research grant from Pfizer Inc.

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ENSURING PATIENT SAFETY IN THE NEW OPERATING THEATRE OF UMMC TRAUMA CENTRE; AN ANAESTHESIOLOGIST NOVICE EXPERIENCE

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ABSTRACT

Patient safety is a serious global healthcare issue. Harm can be caused by a range of errors or adverse events. Therefore, it is vital that the commissioning of a new operating theatre should comply to the highest standard before it is allowed to function. This paper accounts our experience in the commissioning of the University Malaya Medical Centre (UMMC) trauma centre operating theatre (OT) complex in July 2008. We highlighted the problems we faced in adhering to the international standard guidelines. Unanticipated events were handled professionally and solved. With this experience, we hope that the identified problems would provide suggestions for commissioning an operating theatre in the local setting in the future. (*JUMMEC 2009; 12 (2): 83-91*)

KEYWORDS: patient safety, operating theatre commission.

Introduction

Under the 7th Malaysian Plan, a modern trauma and emergency centre was constructed at the forefront of the University Malaya Medical Centre (UMMC). It became operational in 2003. However, the operating theatre (OT) which was designed to compliment urgent emergency surgeries never took off for various reasons. It was not until recently, after an understanding between the UMMC OT committee members that the long awaited functioning of the trauma centre OT came into existence. The need is timely with the increasing emergency surgeries done in the main OT complex.

The Anaesthesiology Department, UMMC was given the responsibility to check and certify that the OT was safe for use. The safety issues included all aspects of patient's care and the needs and services of healthcare staff and supporting staff.

Objective

Patient safety is a serious global healthcare issue. Estimates showed that in developed countries, 10% was harmed while receiving hospital care (1). The harm can be caused by a range of errors or adverse events. Therefore it is vital that the OT inspection should comply to the highest standard and "zero-defect" from avoidable causes.

We hope that we can identify in the local setting common problems associated with commissioning an OT in UMMC.

Methodology

The Anaesthesiology Department team members comprised of a clinical consultant and two medical officers (one senior medical officer and a Master of Anaesthesiology trainee). We were supported by the nursing team which comprised the matron, two sisters, and five staff nurses .

A checklist, which complied to the World Health Organisation (WHO) standards, the recommended minimum OT facilities guidelines set by the Australian and New Zealand College of Anaesthetists (ANZCA) and the standards set by the Ministry of Health of Malaysia (2-6), was prepared by the consultant anaesthesiologist. The checklist was divided into two parts: the physical aspects and the patient related aspects. The inspection

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and ratification was done on the 7th and 8th of July, 2008. The OT started its first case on the 9th of July, 2008.

In this exercise, if the OT was found to be unsatisfactory, surgical operations were postponed to a later date after the major problems were rectified. This consensus was in tandem with upholding patients' safety.

Results

Using the prepared checklist, we double checked with the UMMC Engineering team with the cooperation of the Microbiology Department that they had completed

the steps below (done between weeks 1 June and 30 June, 2008:

1. The OT interior was checked for obvious defects
2. The air distribution within the theatre and between rooms in the theatre suite was satisfactory. The air handling unit supplying the theatre was properly constructed, the theatre was properly constructed, finished and functioning
3. The air change rates in OT and preparation room wa satisfactory
4. Airborne microbial contamination in an empty OT was satisfactory (ICT)

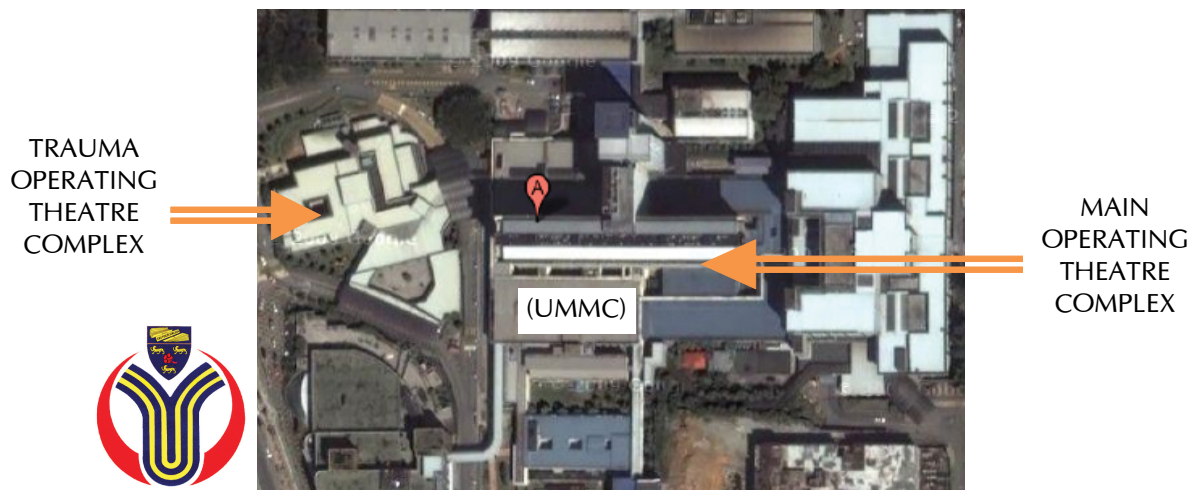


Figure 1: The Universiti Malaya Medical Centre (UMMC) complex

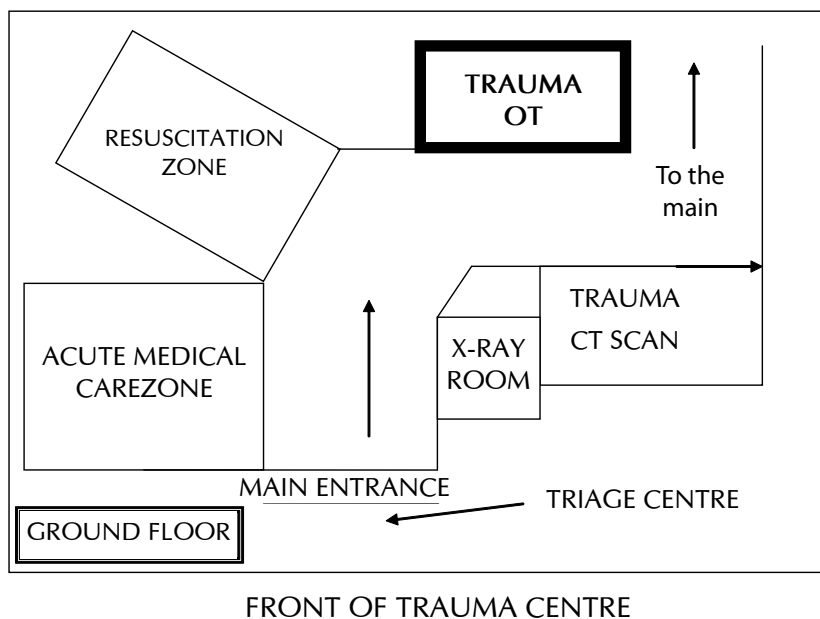


Figure 2: Trauma Operating Theatre (OT) in the Trauma and Emergency Centre

The commissioning checklist was divided into two parts: the physical aspects and the patient related aspects. There were few sub sections that went under vigorous scrutiny. Being abandoned for several

years, there were lots of technical glitches which needed to be rectified. Most of the problems with equipment arose from its non-usage for several years.

Physical Aspects

	7 July 2009		8 July 2009
	Satisfactory Y/N	Immediate Attention and Action	Satisfactory And Rectified
Reception	N	Phone faulty	√
Changing Room	Y		√
Transfer Bay	Y		√
OT 1 safe practice:			
— Warning devices in medical gas pipeline systems, to alarm when bulk gas supplies are low.	N	Engineering	√
— Electrical supply and equipment designed to eliminate risk of microshock.	Y		√
— Emergency lighting and power supply.	N	Engineering	√
— Means of controlling the temperature within the range of 20°C to 28°C.	N	Engineering	√
— A wall clock with a sweep second hand.	N	Not working	√
— Provision for scavenging waste anaesthetic gases and vapours.	N	Engineering	√
— Means of communicating with persons outside theatre.	Y		√
— Separate refrigerators: correct storage of blood and biological products.	Y		√
Standard equipment			
— 12-lead electrocardiograph.	Y		√
— A defibrillator.	Y		√
— A manual, self-inflating resuscitator bag capable of delivering up to 100% oxygen (e.g. Laerdal, Ambu bags).	Y		√
— Central venous pressure sets.	N	OT Staff	√
— Means of infusing intravenous fluids under pressure.	Y		√
— Blood warming apparatus.	Y		√
— Means of insulating the patient against heat loss.	Y		√
— Means of providing or conserving airway humidification.	Y		√
— Intercostal catheter drainage set.	N	OT Staff	√
— Trays suitable for spinal, epidural and regional nerve blocks.	Y		√
— Equipment for difficult intubations.	Y		√
— Patient trolleys capable of rapid tilting.	Y		√
— A refrigerator for the storage of drugs required to be stored in the cold.	N		√

Physical Aspects (continued)

	7 July 2009		8 July 2009
	Satisfactory Y/N	Immediate Attention and Action	Satisfactory And Rectified
Anaesthesia equipment			
1. Each anaesthetic machine must have the following safety features:			
a) An indexed gas connection system.	Y		√
b) A reserve cylinder supply of oxygen and, where appropriate, nitrous oxide.	N	OT Staff	√
c) An oxygen supply pressure warning device.	Y		√
d) An oxygen analyser/monitor with a low oxygen alarm.	Y		√
e) Each anaesthetic machine should include:			
(i) Calibrated vaporisers for accurate delivery of inhalational anaesthetics.	Y		√
(ii) A range of suitable breathing systems.	Y		√
(iii) Breathing systems suitable for paediatric anaesthesia	Y		√
2. An automatic mechanical ventilator, with a disconnection alarm, must be available for each anaesthetised patient.	Y		√
3. Suction apparatus (complying with BS4199, AS2120 or equivalent), including hand pieces (e.g. Yankauer) and a range of endotracheal catheters, for the exclusive use of the anaesthesiologist.	Y		√
4. Alternative suction system	Y		√
5. Standard intubation equipment	Y		√
Recovery Area	Y		√

Patient Related Aspects

	7 July 2009		8 July 2009
	Satisfactory Y/N	Immediate Attention and Action	Satisfactory And Rectified
Identification and transfer flow checklist	Y		√
Linen and clothing	Y		√
Job description	N	Consultant and Matron	√
Patient Selection Criteria	Y		√
Protocols and Guidelines	N	Matron	√

Discussion

Surgery is one of the most complex health interventions to deliver. More than 100 million people in the world receive surgical treatment every year for various reasons. Problems associated with surgical and anaesthetic safety in developed countries account for half of the avoidable adverse events that result in morbidity and mortality (1).

We were fairly satisfied with the audit done on the 7th of July. Most of the important details of the checklist were fulfilled but there were few issues which needed immediate active intervention which is discussed in the subheadings below.

1. Infrastructure

The UMMC Trauma Centre OT mini complex is situated 100m from the main operating theatre complex of the UMMC main building (Figure 1). The infrastructure has been unused since 2003. There were attempts to run it previously, but it did not materialize because of theatre design flaws, which were not anticipated. The piping system and ceiling height were the main culprits of its non functioning status. Hence, the OT was renovated several times. All renovation were completed by March 2007. Human resource was another limiting factor due to the busy day to day running of the main OT. It was almost impossible to

run another facility which was physically apart from the centre of command.

The trauma OT is situated next to the resuscitation zone and opposite the CT scan room on the trauma centre ground floor (Figure 2). It consists of two bedded reception area, two bedded recovery area, two changing room facilities and two functional operating theatres with its sub sections.

It was designed to facilitate urgent emergency surgeries; ideal for efficiency in ensuring optimal management for the patient’s sake. Previously, emergency surgical patients had to travel a distance (with inclining slopes!) from the trauma centre to the main OT complex. This has resulted numerous unwanted events like cardiac arrest during transport. According to Szem *et al*, intra-hospital transfer for in-patients carry a significant morbidity and mortality risk. The morbidity and mortality risk increases in relation to the distance travelling by critically ill patients the further the critically ill patient travels (7).

2. Medical gas system

We had discussions with various divisions of UMMC engineers to sort out the problems that we came across. For example, the selected wall and attached facility gas outlets in both the main OT complex and the mini UMMC trauma centre OT were faulty. This can

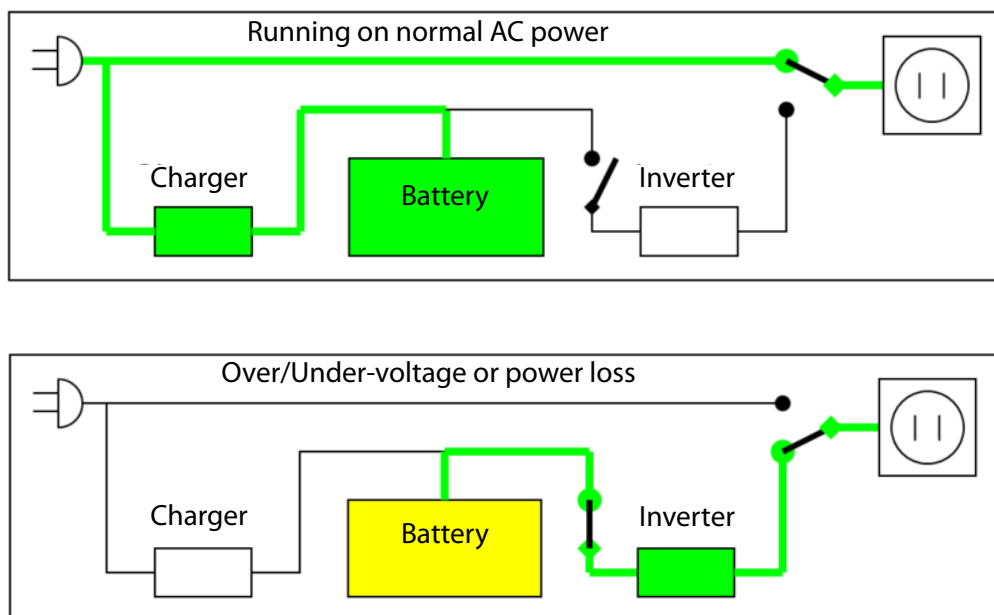


Figure 3: Simple, easy-to-understand diagram of how a Standby UPS works.

be a cardinal sin as malfunctioning of the medical gas systems especially oxygen can endanger patients. We were unable to secure connections (failed “tug test”) to both the oxygen and nitrous oxide gas outlets. One of the oxygen outlets was faulty as no oxygen flow was detected.

After a thorough inspection by the gas engineers, the problem was caused by the faulty hose outlet because it was unused for several years. Hypothetical cross piping that would cause mixture of nitrous oxide and oxygen supply should be detected by the gas analyzer in the General Anaesthetic machine (4).

Another problem that was detected was the scavenging suction system that was not functioning when checked. This is an important component as its malfunction can cause gas pollution, which in turn can create a hazardous environment to the servicing doctors and nurses. It was later discovered that the central line suction pump was faulty and immediately rectified.

3. Electrical safety and system

We were unable to objectively ensure electrical safety for both healthcare workers and patients according to international practice (6, 12). However, we were reassured by the UMMC electrical engineering team that all circuits were grounded and the hazard

of microshock was minimal. We were briefed regarding the Trauma Centre’s electrical safety backup (i.e. backup generator, UPS) in case of power failure. At all times in case of power failure from the main supplier, Tenaga Nasional Berhad, the trauma OT should always have adequate electrical supply by either the backup generator or the UPS system. (Figure 3)

On the 8 July, 2008, we experienced an “unintentional” blackout. It was here that we managed to identify the core electrical supply of the mini OT in the UMMC trauma centre. It was revealed later that the renovation work behind the trauma centre accidentally caused a main cable cut which was quickly repaired.

The OT lights were intermittently malfunctioning caused by the main supply wire. It was also noticed that few light bulbs were faulty. Emergency lights were obviously absent in certain parts of the complex. The UMMC Electrical division was notified and the necessary adjustments were performed immediately.

4. Environmental factors

The temperature, humidity and ventilation systems were inspected and found to be satisfactory. The controls and indicator were working well. However,

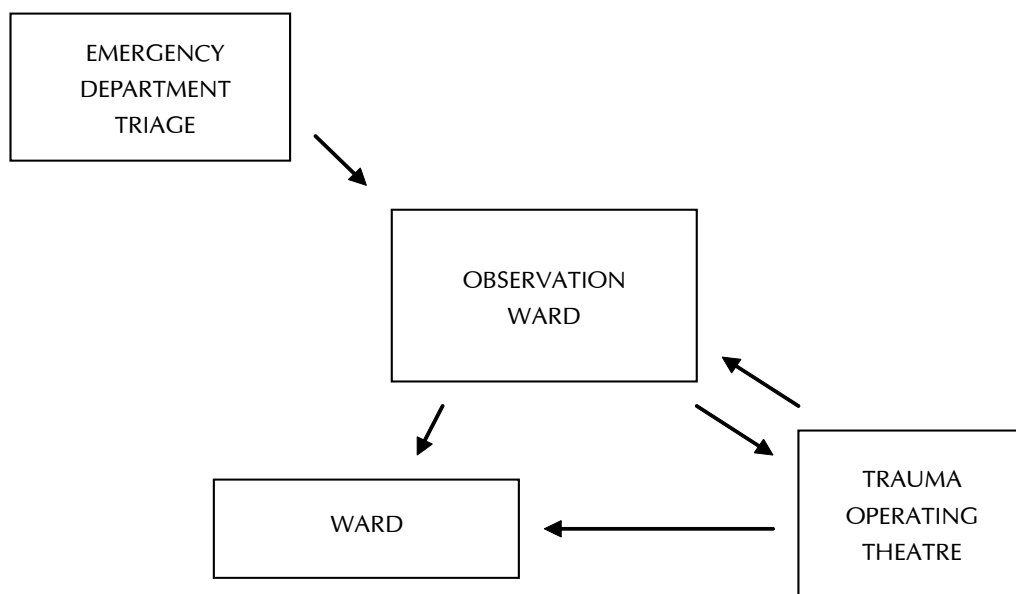


Figure 4: Patient flow from triage to Trauma OT (not to scale)

due to power failure of the Trauma Centre on 8 July, 2008, because of ongoing construction works in the UMMC compound, the air conditioning system was not functioning. This caused high humidity and moderate temperature rise that caused both theatres to be wet and hazardous. The first case planned on the 9th of July nearly did not materialize. With the help from the engineering department, the failure was rectified.

Fire extinguishers were in good condition and placed at critical areas. Emergency exits were also easily identified and accessible.

5. Equipment

Both theatres were equipped with two Datex Ohmeda Aestiva 5 anaesthetic machines. They were brand new and we checked the functional status thoroughly by following the standard operating manual provided by the manufacturer. The general manager of the company that supplied the machines was also present. He counter checked and confirmed that the machines were safe to be used on patients.

Other monitoring devices were also inspected and certified fit to be used. All the monitoring devices were in accordance with the minimal monitoring standards as prescribed by ANZCA and Ministry of Health, Malaysia (3, 5).

Besides that, the intubation trolley, resuscitation trolley and the difficult airway trolley were strictly audited and checked to ensure that every single equipment was available and in good working condition.

6. Patient-related aspects checklist

The second part of the checklist was patient-related where the issues were on the administrative in nature. Effective communication between surgeons, anaesthetists and OT staff is vital for optimal patient care (11). The booking system and patient flow were thoroughly discussed between the Anaesthesiology Consultant with the operating theatre staff. Accurate documentation was necessary and it was to be complimented by smooth patient flow (Figure 4).

As agreed in the earlier meetings of the OT committee, when the OT is found to be satisfactory, it would

undergo a two month trial. Patients who were to be operated in this theatre would adhere to few selection guidelines (Table 1). It was hoped that all minor details would be sorted out before the OT could accept "TRUE" trauma surgeries.

Table 1: Patient Selection for Trauma OT

Criteria	
American Society of Anaesthesiologist (ASA) Class	I and II
Patient selection	Adult 18 and above Children 2 – 5: needs discussion Children < 2: not suitable
Consent	Next of kin not allowed
Duration	Maximum 2 hours
Type of surgery	Haemodynamically stable patients with established diagnosis Example of surgeries: Surgery: Appendectomy Wound debridement for leg ulcers Toilet and Suturing for cuts ICP monitor insertion Burr Hole Orthopaedics: Open fracture wound debridement Diabetic foot ulcer debridement
Type of anaesthesia	General Anaesthesia without invasive monitoring Regional Anaesthesia Local Anaesthesia
	All cases posted must be approved by the Consultant Anaesthesiologist and Consultant of the Emergency Department

Implementation

On the 9th of July, 2008, there were two cases booked by the general surgery team. Only one case fulfilled the strict criteria (Table 1). The case was informed to the consultant anaesthetist in charge and she gave the green light. However, it was discovered that the theatres were all wet as a result of the impaired air conditioning. The temperature in the OT was 28°C and humidity at 90% because of the power failure in the trauma centre complex the previous day. The repair work was still in progress on the 9th of July, 2008. The UMMC engineers rectified the problem by 10.30 a.m. and we were satisfied with the theatre's condition at 11.45 a.m.

A 39 year old Cambodian lady ASA 1 was planned for appendicectomy after the surgeons confirmed her clinical and investigative findings. She was admitted at 10.15 p.m. the previous night and placed in the observation ward. She was assessed by the anaesthesia trainee early in the following morning. The patient was anaesthetized at 12.10 p.m. The surgery was done within the one hour window and safely extubated. It was uneventful.

She was haemodynamically stable in the recovery area and did not require any further analgesics during her 30-minute observation there. She was later brought to the surgical ward at 2.30 p.m.

An immediate "post mortem" was done by all the staff in charge to trouble shoot and review all problems that impaired patient flow throughout the surgery. It was recorded down on a designated logbook for audit and future reference.

Conclusion

A patient's safety remains as the anaesthesiologists' main priority as perioperative physician. The anaesthesiologist takes full responsibility of the patient as soon as he or she steps into an OT (2, 5). This would concur to the Joint Commission International (JCI) accreditation philosophy in setting standards for hospitals focused on one goal: raising the safety and quality of care to the highest possible level (13).

Managing an OT complex may appear simple but there are many aspects to be looked into prior to starting any case. The first few chapters in any standard Anaesthesiology textbooks emphasise these issues in detail. Perfection is mandatory and morbidities and mortalities should be prevented (8, 9).

Efficient teamwork is vital to success in any interdisciplinary initiatives. In operating theatres, the cooperation and multilateral understanding between the doctors, nurses, supporting staff and ground staff ensures smooth operational OT flow (10). Preventing unnecessary delay in patient care will contribute to better outcome as well as reducing economic costs. Hopefully, the opening of UMMC trauma centre OT complex will pave way for more efficient use of time, optimal patient safety and minimize unnecessary resource allocation for the local setting.

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CARBIMAZOLE-INDUCED APLASTIC ANAEMIA—A CASE REPORT

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ABSTRACT

Antithyroid drugs have been used for more than 50 years for the management of hyperthyroidism. Most patients tolerate treatment well, but some may develop rare life threatening side effects such as agranulocytosis and aplastic anaemia. Clinical experience with the latter condition is extremely limited. We report on a case of carbimazole-induced aplastic anaemia caused by hypocellular bone marrow and associated plasmacytosis in a thyrotoxic patient chronically treated with carbimazole. This resolved after substitution with propylthiouracil. The clinical course was complicated by neutropaenic septicaemia and atrial fibrillation. (*JUMMEC 2009; 12 (2): 92-95*)

KEYWORDS: *thyrotoxicosis, carbimazole, aplastic anaemia, plasmacytosis*

Introduction

A 37-year old single Malay male who smoked 20 cigarettes a day, presented to us on the 9 February, 2007, with a two week history of fever, chills, sore throat, lethargy, decreased exercise tolerance, dyspnoea, vomiting, diarrhoea, loss of appetite and loss of six kilograms in weight.

He had been diagnosed with Graves' disease and thyrotoxicosis in 1996 and treated with carbimazole and propranolol by his general practitioner, but he had not been compliant and stopped treatment in December 2006. He was initially presented to another tertiary centre on 19 January, 2007, and was noted to be thyrotoxic and in atrial fibrillation. He was commenced on carbimazole 20 mg BD and propranolol 20 mg TDS and discharged. Full blood counts (FBC) at this time showed haemoglobin (Hb) 14.9 g/dL, leucocytes (WC) 6.7×10^9 /L and platelets (Plt) 201×10^9 /L. He was discharged the next day and became unwell a week later.

Methodology

On admission, he was alert and comfortable, but dehydrated, tremulous, and febrile at 38.3°C. His throat was erythematous with a small right cervical lymph node. A small diffuse goiter was present and lid lag was noted, but there were no other eye signs. He was in atrial fibrillation with an apical rate of 146/min, but reverted spontaneously to sinus rhythm of 90/min. There was no evidence of cardiac decompensation. TSH <0.01 mIU/L, free T4 95.3 pmol/L, free T3 23.2 pmol/L. Full blood count showed Hb 16.3 g/dL, WC

1.6×10^9 /L, ANC 0.8×10^9 /L, Plt 33×10^9 /L. Chest radiograph was normal. Carbimazole was discontinued, and he was commenced on propylthiouracil 200 mg QID, Lugol's iodine 10 drops TDS, propranolol 20 mg TDS and intravenous hydration. Antibiotic therapy with piperacillin/tazobactam 4.5 g TDS was started.

The patient's general condition improved and he was subsequently afebrile. Blood, urine and sputum cultures were negative. Platelets fell to 7×10^9 /L on 12 February, 2007, and he was transfused with four units of platelets although there was no bleeding tendency.

Bone marrow aspirate and trephine (BMAT) biopsy of the right posterior iliac crest on 13 February, 2007, revealed a few marrow fragments which were very hypocellular with no clumps within the stromal tissue. Lymphocytes and plasma cells were seen (Figure 1). Erythropoiesis and granulopoiesis were markedly depressed with dysplastic granulopoietic maturation. Megakaryocytes were virtually absent. No clusters of abnormal cells were seen and there was no increase of reticulin fibres. Granulocyte colony stimulating factor (G-CSF) was not given at this stage after discussion with our haematology colleagues.

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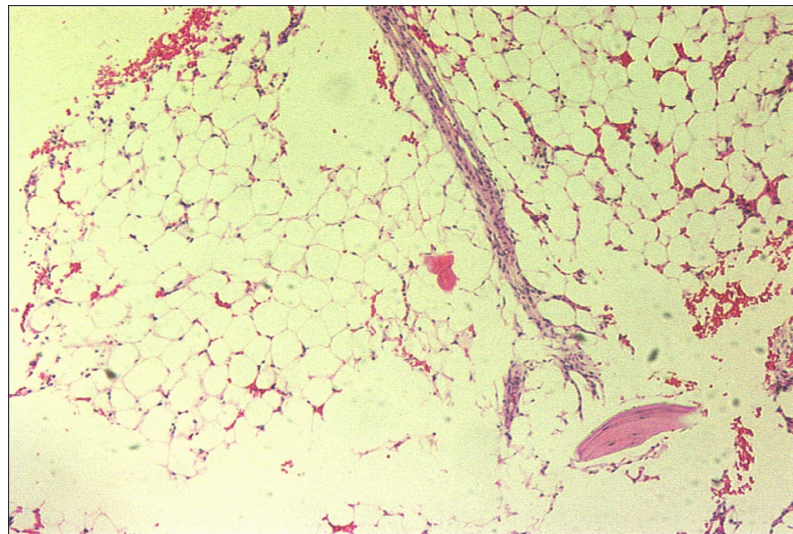


Figure 1: Hypocellular marrow (Trephine biopsy)

On 14 February, 2007, Lugol's Iodine was stopped. His temperature spiked to 38.2 °C two days later, and he became hypotensive. Septic work up was repeated and his antibiotics was changed to imipenem 500 mg TDS. Propranolol was discontinued. He recovered and remained well subsequently, but had to be recommenced on propranolol on 21 February, 2007, after he was noted to be having paroxysms of atrial fibrillation. Repeat blood cultures were negative. He was discharged the same day with ciprofloxacin 500mg TDS and amoxicillin and clavulanic acid 625mg TDS. Hb was 11.8 g/dL, WC 1.6×10^9 /L, ANC 0.06×10^9 /L, Plt 20×10^9 /L.

His blood counts normalized on 12 March 2007—30 days after initial presentation (Figure 2 and 3). Transthoracic echocardiogram was normal with good left ventricular ejection fraction of 70%. He was later anticoagulated with warfarin after his platelet count had recovered. His antithyroid drugs were gradually tapered and he subsequently received radioactive Iodine 131 therapy at a dose of 10 mCi on 5 November, 2007, which rendered him euthyroid.

Discussion

The infrequent and often serious idiosyncratic drug reaction of agranulocytosis (ANC $< 0.5 \times 10^9$ /L) is a well recognized side effect (0.2-0.5%) of treatment with the antithyroid drugs (ATD's) carbimazole, methimazole and propylthiouracil (1). However, aplastic anemia is rare with only 34 cases reported and about 17

adequately documented, not including this case. It is thought to be a humoral autoimmune response which results in transient bone marrow aplasia. Two cases have been reported with Propylthiouracil. There have been two fatalities reported from intracerebral haemorrhage (2-6).

Patients usually present with symptoms of agranulocytosis between one and four months after commencing ATD's. Unusually, in this case there is history of long term carbimazole use although this has been described in other reports (7). Laboratory findings are of aplasia of the bone marrow and pancytopenia in the peripheral blood. Recovery of all cell lines occurred two to five weeks after discontinuing the offending drug. The prognosis with carbimazole-induced aplastic anaemia is better than with other forms of drug induced aplastic anaemia. The prognosis is linked to the degree of hypoplasia in the marrow.(2, 4).

The role of G-CSF in aiding granulocyte recovery in ATD-induced aplastic anaemia is not clear as it has been used in only three cases. Reports suggest that it may be more effective in moderate than in severe cases. No other predictors of response are known (4, 8). Due to a delay in BMAT findings, G-CSF was not given on initial presentation and was felt unnecessary later as the patient remained well clinically. Propylthiouracil was used guardedly as the patient was still markedly thyrotoxic and at risk of cardiac arrhythmias. Lithium and cholestyramine have been

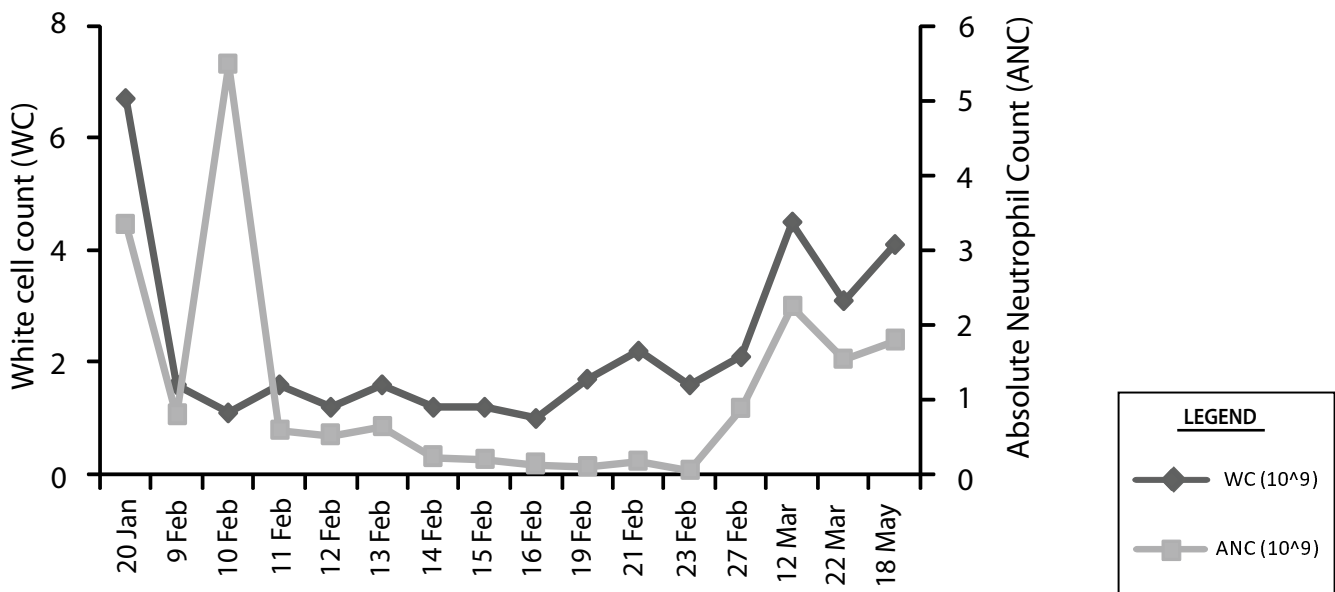


Figure 2: Leucocyte and absolute neutrophil count trend

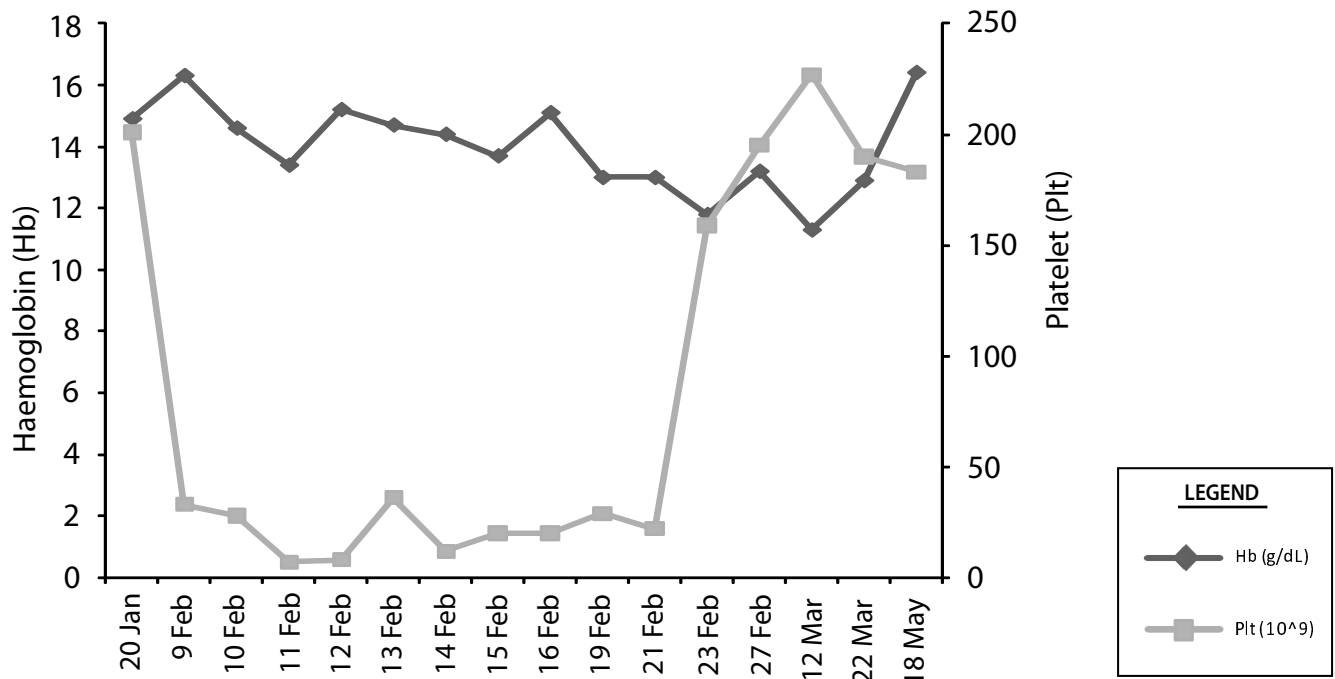


Figure 3: Haemoglobin and platelet trend

used to replace conventional ATD's to prevent recurrent thyrotoxicosis. Of interest, lithium may have an effect of promoting granulopoiesis (4, 8). Corticosteroids have been used successfully, but were withheld here due to the possibility of serious underlying infection (9).

To our knowledge, there are only two reports of plasmacytosis associated with carbimazole-induced aplastic anaemia. Both patients recovered after drug withdrawal with complete marrow recovery. The presence of plasma cells lends weight to an

immunogenic aetiology of this rare complication of ATD use (10, 11).

Routine FBC is not advocated in patients commencing on ATD's. It is important to provide verbal or written instructions to patients to quickly report symptoms of agranulocytosis, which predominate and can present rapidly in an outpatient setting.

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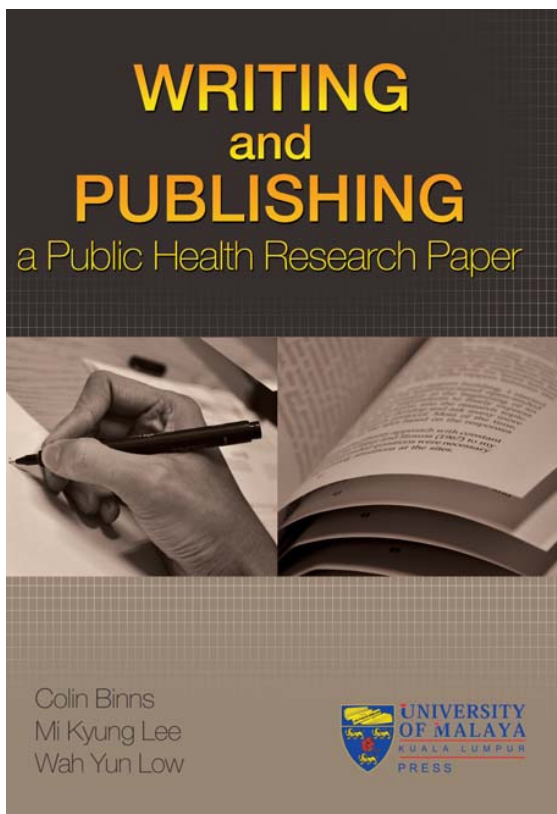
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Authors: Colin Binns, Mi Kyung Lee & Wah Yun Low

ISBN: 978-983-100-483-8

Price: US\$30

Publisher: University of Malaya Press

Website: <http://umpress.um.edu.my>

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