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Portrait of Jean Borel, discoverer of cyclosporine A by Sir Roy Calne.

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TOWARDS MORE RATIONAL PRESCRIBING

The articles in JUMMEC deal with a wide variety of issues; foremost amongst them, is the discussion on the rational use of drugs in treating many illnesses and medical conditions.

Certainly, drug therapy is critical for the treatment of many illnesses and conditions but in the present climate of rising cost of care and limited resources, we should ask ourselves if we are getting value for our money; in other words, there should be more rational use of drugs. Antibiotics are amongst one of the more frequently prescribed drugs. In fact, it had been reported to account for as much as 50% of some hospital pharmacy budgets. The widespread use of antibiotics had lead to the emergence and spread of microbes, that are resistant to cheap and effective "first-line" drugs.

Resistance to antimicrobials is a natural biological phenomenon – a case of survival if you like. Factors that contribute to this emergence of drug resistance include human practices ranging from poor prescribing, unnecessary or not indicated use, under-dosing or using for too short a duration, poor compliance on the part of the patient, as well as veterinary prescribing in animal husbandry.

As seen from the paper on antimicrobial susceptibility of *Pseudomonas aeruginosa,* susceptibility of this organism to the newer, more expensive antimicrobials has already been compromised. Fortunately, community-acquired *Pseudomonas aeruginosa* infections are still 100% susceptible. That being the case, every effort should be made to prevent further emergence of more drug-resistant organisms.

This problem of antimicrobial resistance has reached an alarming stage of global importance, that in September 2001, WHO launched the first global strategy to combat the problem of drug resistance. The University of Malaya Medical Centre should be commended for having developed an antibiotic guideline for use in the hospital – to enhance and encourage more rational antibiotic prescribing.

Besides drug resistance, drug cost is also a matter of huge concern in any health care organization. Here again, it is timely that efforts have been made to relook at the cost of drugs. An original article compared the use of risperidone with olanzapine in the treatment of schizophrenia.

Besides cost being the underlying principle in drug prescribing, efficacy and safety should be important considerations as well. While steroids would seem a less expensive choice as an agent for immunosuppression after renal transplantation, there are other alternatives, albeit more expensive, which would be safer, less toxic and more efficacious. In the review article, discussion was centred on the withdrawal or avoidance of use of steroids after renal transplantation.

Complementary medicine is currently in vogue although much of it has not been well understood nor has it been scientifically studied. Substances that are ingested, either supplements or remedies, have not been subjected to the same rigorous processes that new drugs have to undergo when seeking registration. The paper on cytoprotective effect of honey with extracts of *Chromolaena odorata* L. a herb, is certainly worth further reading. Obviously for such herbs to be deemed efficacious and of medicinal value would require well-designed, blinded randomized-control trials performed on humans.

Cardiovascular disease (CVD) is very prevalent in Malaysia. It is still the number one cause of medically certified deaths in our country. Interest in aetiological factors, one of which is obesity, is being extensively studied. It is interesting to note in the paper, "Body fat comparison between basketball and netball players in Malaysia" that even amongst national athletes, in particular, female basketball and netball players, their average percentage of body fat, is higher than the desired average for elite sportsmen.

Angina is one of the presenting symptoms of coronary heart disease. However, trying to reach a diagnosis of angina could be quite complicated and fraught with uncertainties. The use of simple neural network architecture to diagnose angina was discussed in some detail in this issue.

While CVD is the number one killer in Malaysia, deaths due to road traffic accidents (RTA) are not far behind. In fact, year after year, we read about the large number of RTA deaths. There could be many contributing factors to this, and poor visual acuity is certainly a possible cause. It would appear from the paper on visual defects amongst commercial vehicles drivers that indeed visual defects are under-diagnosed. Greater efforts should be made to detect visual defects, not only amongst commercial vehicle drivers but all drivers, too.

Finally, it is encouraging to note that maternal mortality in Malaysia had declined very significantly over the last 50 years. However, this is no reason to rest on our laurels. It had been discussed in "Measuring maternal mortality in Malaysia" that we should be looking at the lifetime risk of maternal mortality and not at maternal mortality ratio alone. More importantly, the question is, could maternal mortality be further reduced. And now, with more interest in maternal mortality and so many clinical trials being conducted that include a significant number of women, it can be said that the era of women, has finally arrived.

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STEROID WITHDRAWAL OR AVOIDANCE IN RENAL TRANSPLANT RECIPIENTS

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ABSTRACT: Steroids remain an important component of maintenance immunosuppression after renal transplantation. Their anti-inflammatory action is partly due to the sequestration of CD4+ lymphocytes in the reticuloendothelial system. Steroids bind to intracellular receptors and the resulting steroid-receptor complex alters the transcription of cytokines by binding to glucocorticoid response elements on DNA. Transcription factors whose actions are altered by glucocorticoids include activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). The main cytokines whose production by antigen-presenting cells is inhibited by steroids are interleukin-1 (IL-1), required for helper T-cell activation, and IL-6, required for B-cell activation. Other pro-inflammatory cytokines such as interferon gamma and tumour necrosis factor are also inhibited. This multiplicity of immunosuppressive actions is not fully replicated by other immunosuppressants. However, there are concerns about the long-term side effects of steroids. This review will examine the attempts at steroid withdrawal or steroid avoidance in renal transplant patients. ***(JUMMEC 2006; 9(1): 2-6)***

KEYWORDS: steroid withdrawal, renal transplantation, immunosuppressants

Introduction

Steroids remain an important component of maintenance immunosuppression after renal transplantation. While still incompletely understood, recent discoveries have provided insights into their mechanisms of action (1). Their anti-inflammatory action is partly due to the sequestration of CD4+ lymphocytes in the reticuloendothelial system. Steroids bind to intracellular receptors and the resulting steroid-receptor complex alters the transcription of cytokines by binding to glucocorticoid response elements on DNA. Transcription factors whose actions are altered by glucocorticoids include activating protein-1 (AP-1) and nuclear factor-κB (NF-κB). The main cytokines whose production by antigen-presenting cells is inhibited by steroids are interleukin-1 (IL-1), required for helper T-cell activation, and IL-6, required for B-cell activation. Other pro-inflammatory cytokines such as interferon gamma and tumour necrosis factor are also inhibited. This multiplicity of immunosuppressive actions is not fully replicated by other immunosuppressants.

However, there are concerns about the long-term side effects of steroids. These include hyperglycaemia, dyslipidaemia, hypertension, truncal obesity, cushigoid features, osteoporosis, aseptic bone necrosis, growth disturbances in children and cataracts. The first four factors may contribute to cardiovascular disease, a leading cause of mortality and morbidity in transplant patients (2). The cost of steroid-related side effects in the US is estimated at $5,300 per patient (3).

This review will examine the attempts at steroid withdrawal or steroid avoidance in renal transplant patients. Concomitant maintenance immunosuppressants may include calcineurin inhibitors (cyclosporine, tacrolimus), antimetabolites (azathioprine, mycophenolate mofetil) or sirolimus, which inhibits the mammalian target of rapamycin (mTOR). During the initial, high-risk post-transplant period, patients may also receive induction therapy with OKT3 (an anti-CD3 monoclonal antibody), antithymocyte (ATG) or antilymphocyte (ALG) globulins, or the IL2-receptor antagonists, basiliximab or daclizumab.

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Cyclosporine/azathioprine-based regimes

Cyclosporine gained widespread usage in renal transplantation after it was shown to improve short term graft survival compared to azathioprine (4,5,6). Steroid withdrawal in the early (6-12 days) post-transplant period was abandoned after it was found to increase the rate of acute rejection (AR) (7). A meta-analysis of randomized controlled trials (RCT's) of late steroid withdrawal with this regime examined nine studies with a total of 1,461 patients (8). The authors found a 14 per cent increase in AR and a 40% increase in graft failure in the steroid withdrawal group. Steroid withdrawal from patients with stable graft function at 1-6 years post-transplant (9). While there were no documented AR episodes, serum creatinine at 1-year post-withdrawal was significantly higher than in the control steroid maintenance group. In the largest RCT, worse 5-year graft survival in the steroid withdrawal group was found, although this effect was not detected on shorter follow-up (10). These two studies suggest that apart from precipitating AR, steroid withdrawal may also impair graft function, possibly by increasing chronic rejection. The study (10) also emphasizes the importance of long-term follow-up in these studies. Because of these results, enthusiasm for steroid withdrawal in patients on this regime has waned.

However, a recent trial studied the possibility of steroid withdrawal with the addition of an anti-IL2 receptor antibody. One hundred fifty-seven patients on cyclosporine and azathioprine were randomized to receive induction with basiliximab or placebo. Steroids were withdrawn five months post-transplant. Patients in the basiliximab group had higher success in steroid withdrawal, fewer AR's (25.3% at 1 year) and fewer graft losses (11).

Cyclosporine/mycophenolate mofetil-based regimes

Mycophenolate mofetil (MMF) is an antimetabolite which is superior to azathioprine in preventing AR (12,13,14). Two major studies have looked at steroid withdrawal in cyclosporine/MMF-based regimes. The European trial (15) randomized 500 patients to standard therapy or to steroid withdrawal after 12 weeks of half-dose prednisolone (low/stop group). They found a higher AR rate at 12 months follow-up in the low/stop group. Interestingly, there was no difference between the groups among patients who received induction therapy with OKT3 or antithymocyte globulin. The US trial (16) recruited primary transplant patients with no early AR and randomized them to standard therapy or steroid withdrawal at three months post-transplant. The study was terminated prematurely when the steroid withdrawal group was found to have a much higher 1-year AR rate (30.8% vs 9.8%). This difference was especially pronounced among the African-American subjects. However, several recent smaller RCTs have found no increase in AR after steroid withdrawal (17,18,19).

Tacrolimus-based regimes

Tacrolimus is a calcineurin inhibitor which is superior to cyclosporine in preventing AR (20,21,22) and preserving graft function (23). There have been no large RCTs of steroid withdrawal in patients on tacrolimus-based regime. A retrospective analysis by the Pittsburgh group of 795 patients on tacrolimus and azathioprine or MMF found better graft survival in patients in whom steroids were withdrawn (24). However, there may be bias as these patients had lower immunologic risks compared to those in whom steroids were continued. A small RCT (25) involving patients with low immunologic risks found no AR and 100 per cent graft survival in both steroid withdrawal and maintenance group at 24-months' follow-up. However, four out of 48 patients developed rising creatinine after steroid withdrawal, which recovered after steroids were restarted.

Steroid sparing and avoidance protocols

A significant disadvantage of late steroid withdrawal is that some steroid side effects, such as osteopaenia, have their greatest effects during the early post-transplant period, when high doses of steroids are used. In addition, steroids may affect the development of tolerance by inhibiting T-cell apoptosis (26). The development of powerful induction immunosuppressive agents has stimulated interest in the use of steroids for only a limited period (i.e., a few days) or not at all.

Since the mid-nineties, a Danish centre has been using a steroid-free protocol consisting of ATG for ten days together with maintenance cyclosporine and MMF. A review of 100 consecutive transplant recipients showed a 1- and 4-year graft survival of 97% and 82% respectively (27). There were only 13 episodes of AR, mostly in the first three months, and all were successfully reversed. A steroid-free regime is also possible with Campath 1H, a lymphocyte-depleting, humanized anti-CD52 monoclonal antibody. With two doses of Campath 1H and low dose maintenance cyclosporine, the Cambridge group was able to achieve graft survival of 29/31 at a mean follow-up of 21 months, with six episodes of AR (28).

Several studies have looked at regimes with anti-IL2 receptor antibody induction. With tacrolimus/MMF/anti-IL2 receptor antibody immunosuppression, steroid-free patients had a higher AR rate at six months post-transplant, but the difference disappeared by 12 months. However, it is unclear whether the patients

were randomized, and the mean follow-up period was short (29).

A case series of patients receiving daclizumab induction and maintained on cyclosporine and MMF was published (30). The 1-year graft survival was 89 per cent with an AR rate of 25 per cent, most of which were steroid-responsive and the majority of which occurred in the first month. However, by the end of the first year, a third of the patients required maintenance steroids. Further follow-up at three years post-transplant showed good graft survival and graft function, and few late rejections (31). A prospective RCT is in progress comparing daclizumab induction and two days of steroids with no daclizumab and 16 weeks of steroids. Maintenace immunosuppression is with tacrolimus and MMF. An interim analysis at a mean follow-up of 11 months found no difference in AR rates between the two groups (32).

Initial experience with basiliximab has been similarly positive. A comparative study was done on a 4-day steroid regime with steroid maintenance, with concomitant cyclosporine, MMF and basiliximab induction (33). At six months' follow-up, there was no difference in AR rate and serum creatinine between the two groups. A randomized study of 27 patients receiving basiliximab/cyclosporine/MMF to maintenance steroids or no steroids was carried out (34). The no steroids group also received two extra doses of basiliximab at 60 and 64 days post-transplant. There were no differences in AR and creatinine clearance after follow-up for one year.

Sirolimus-based regimes

Sirolimus is a relatively new immunosuppressant with a unique target (mTOR). There has not yet been RCTs of steroid withdrawal using a sirolimus-based regime. In an uncontrolled observational study, 75.4 per cent of 156 patients on cyclosporine and sirolimus had their steroids successfully withdrawn at one week to two years post-transplant. At three years, the AR rate was 6.4 per cent, the chronic rejection rate was 5.1 per cent and graft loss occurred in 7.7 per cent (35).

Metabolic benefits of steroid withdrawal

The main reason for steroid withdrawal is the purported metabolic benefits. This assumption was recently challenged by the findings of a retrospective review (36). After a mean follow-up of 7.6 years, the authors found no further metabolic benefits of prednisolone reduction to below 10 mg every other day. In addition, most of the early metabolic benefits of steroid withdrawal were not sustained over longer periods.

Identifying patients suitable for steroid withdrawal/avoidance

The RCTs of steroid withdrawal cannot give us clear-cut answers as to who can undergo steroid withdrawal or be started on a steroid-free protocol. The studies vary greatly in the patients' characteristic, concomitant immunosuppression, timing and rate of steroid withdrawal, duration of follow-up and study end-points. Thus, the consideration of the risk:benefit ratio should be individualized, based on the patients' immunologic profile, transplant history and concomitant medications, the severity of steroid-related side effects, coexisting cardiovascular risk factors, and the opportunity for a retransplant should the current graft fail.

Thus, prime candidates for steroid withdrawal or avoidance would be a non-sensitised recipient of a well-matched graft from a living donor, without delayed graft function or acute rejections, and who has good, stable graft function. Steroid withdrawal or avoidance should also be considered in patients who already suffer from significant steroid-related side effects (such as osteopaenia, or growth retardation in children) or who have significant coexisting cardiovascular risk factors, especially diabetes mellitus, dyslipidaemias, hypertension or a strong family history of cardiovascular disease. Few patients are likely to meet all these criteria, so the eventual decision should be made after careful consideration by the clinician and the patient.

Conclusion

In conclusion, newer, more powerful immunosuppressants have reduced the risk of steroid withdrawal or avoidance. Many of the studies on these agents are small, short and have not been published in peer-reviewed journals. In addition, the metabolic benefits of steroid withdrawal may not be sustained nor superior to low dose maintenance steroids. Therefore, the overall risk:benefit ratio should be individualized for each patient.

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CYTOPROTECTIVE EFFECTS OF HONEY IN COMBINATION WITH AQUEOUS AND ETHANOL EXTRACTS FROM *CHROMOLAENA ODORATA* L. (*EUPATORIUM ODORATUM* L.) IN RATS

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ABSTRACT: Six groups of adult *Sprague-Dawley* rats were orally administered with a variety of treatments to elucidate their cytoprotective effects. Absolute ethanol combined with HCl was used to induce gastric lesions in rats. Aqueous and ethanol extracts of *Chromolaena odorata*, a famous folk herb for treating skin wounds were evaluated to determine their protective effect on gastric mucosa. In this study, aqueous extract and ethanol extract of *C. odorata* were combined with honey. In addition, honey alone and honey combined with cimetidine were also evaluated. Rat stomachs were examined grossly and histologically. Results were expressed as inhibition percentage. The honey and aqueous extract combination showed the highest inhibition percentage (72.67%) followed by honey and ethanol extract (58.92%), honey and cimetidine (56.55%) and the lowest was honey alone (46.74%). However, there were no significant differences between the effects of aqueous and ethanol extracts of *C. odorata* and honey in promoting cytoprotective effects and this may be due to the small sample size. Nevertheless, these results suggest that *C. odorata* and honey may be beneficial in treating induced gastric mucosal injury. *(JUMMEC 2006; 9(1): 7-13)*

KEYWORDS: Honey, cimetidine, ulcer, *Chromolaena odorata*, rats

Introduction

The definition of cytoprotective effects could be interpreted as the capability of a compound to prevent the formation of gastric mucosa necrosis produced by a variety of necrotizing agents, without reducing acid secretion. The exact mechanism of gastric cytoprotective effects in maintaining the cellular integrity of the gastric mucosa that are subjected to strong irritants is unknown (1).

In humans, the gastric mucosa is often bombarded with aggressive exogenous and endogenous luminal agents. Therefore, the body has its own cytoprotective properties to retain mucosal layer integrity and reduce the frequency of developing erosions, ulcers, and hemorrhages (2).

For example, glutathione, which is abundant in the stomach, was demonstrated to be protective against ethanol-induced gastric mucosal damage by scavenging free radicals (3). Besides glutathione, prostaglandin activity (1) and activation of Protease-activated receptor-2 (PAR-2) also exert a cytoprotective effect (4).

In a healthy human stomach, an efficient equilibrium exists between the potential for gastric acid and pepsin to damage gastric mucosal cells and the ability of these gastric cells to protect themselves from injury (5). There are many reasons which lead to gastric mucosal injury that consequently caused the exposure of hydrochloric acids and pepsin to the underlying epithelial cells. It was suggested that one reason is that reactive oxygen species (ROS) can chemically induce gastric mucosal injury. Furthermore, it was investigated that ROS may cause DNA fragmentation (5).

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A report suggested that natural honey is able to protect the rat stomach and also able to accelerate healing against acute ethanol- and indomethacin-gastric lesions (6). Another study also explained the effects of honey in gastroprotective activity. The report mentioned that the mechanism of gastroprotective properties in honey against ethanol-induced gastric haemorrhagic lesions is mediated through sulfhydryl (SH)-sensitive processes. In referring to the previous statement, it was suggested that honey has many similar features to sucralfate, which is a locally acting anti-ulcer drug. Honey and sucralfate have both been shown to deliver protection against ethanol-induced gastric haemorrhagic lesions by preventing depletion of endogenous non-protein SH mainly in the form of glutathione (GSH). Consequently both honey and sucralfate have the ability to inhibit vascular permeability changes and vascular damage which are induced by ethanol (7).

Besides that, the constituents of catalase in honey are able to promote protection against the toxic effects of oxygen-derived free radicals (ODFRs) and abolish the increment of endothelial cell permeability (7).

Chromolaena odorata (L) King and Robinson (formerly *Eupatorium odoratum*), belongs to the family Asteraceae and is a native plant of South and Central America. This species has, however, successfully spread to other warm and humid tropical regions such as South Africa, Vietnam, India, Indonesia, Malaysia, Sri Lanka and the Philippines (8,9).

It is a herbaceous perennial, which grows into a big bushy herb or subshrub and can reach up to the height of three meters in open area (8,10,11). *C. odorata* is believed to be a poisonous plant with exceptionally high levels of nitrate, which is five to six times above the toxic level especially in the leaves and young shoots (12). However, *C. odorata* is a famous herbal remedy in treating wounds. In Vietnam, the fresh leaves and extracts of the plant have been long used in treating burns, soft tissues and skin infections (13).

Even though there are not many studies done to evaluate the use of *C. odorata* extracts in preventing ulcer, there are claims that *C. odorata* can be used as treatment for abdominal disorders. A study also showed that methanol extract of the leaves of *C. odorata* possess anti-inflammatory, antipyretic and antispastimodic properties. The study also established that the extract attributed to antimotility and anti-diarrheal effects (14).

The leaves of *C. odorata* have the maximum amount of allelochemicals (15). A study in Vietnam showed that the aqueous extract of the leaf consisted of flavonoids (salvigenin, sakuranetin, isosakuranetin, kaempferide, betulenol, 2-5-7-3 tetra-O-methyl quercetagetin, tamarixetin, and two chalcones, odoratin, and its alcoholic compound), essential oils (geyren, bornyl acetate, beta eubeden), saponin triterpenoids, tannins, organic acids, and numerous trace substances (16).

Another study showed that the crude ethanol extract of *C. odorata* contains phenolic acids (protocatechuic, p-hydroxybenzoic, p-coumaric, ferulic and vanilic acids) and complex mixtures of lipophilic flavonoid aglycones (flavanones, flavonols, flavones and chalcones) (17).

In this study, a comparison was made between aqueous and ethanol extracts of *C. odorata* mixed with honey to determine which method of extraction resulted in better cytoprotective effect to the gastric mucosa. Cimetidine, a H_2-receptor antagonist was also mixed with honey and evaluated for its cytoprotective effect.

Materials and Methods

Honey

The honey used in this study was pure, unprocessed, unboiled and commercialized, purchased from the Faculty of Agriculture, University Putra Malaysia, Serdang, Selangor, Malaysia. The honey was filtered before use.

C. odorata

Leaves were separated from the stalk and were dried in an oven at 50°C for 5-7 days or until the leaves were fully dried. Then the leaves were ground. The aqueous extract of *C. odorata* was prepared by placing ground leaves in a conical flask. Sterile water was added such that for every 1 g of ground leaves was 20 ml of sterile water (1:20). Then the flask containing the ingredients was left and the contents macerated for three hours on a hot plate. The ethanol extract of *C. odorata* was prepared by placing the ground leaves in a conical flask and 96% denatured ethanol was added in the proportion of 1 g of ground leaves to 20 ml of 96% denatured ethanol (1:20). The flask containing the ingredients was then left for maceration for approximately 5-7 days at room temperature.

Next, the crude extracts from aqueous and ethanol extractions were filtered with a filter funnel to remove the filtrate. After that, the filtered extracts were concentrated with the aid of a rotary evaporator at 60°C. Finally, the concentrated extracts were freeze-dried to produce a powdery form of the extracts, which were stored at -20°C until use.

Preparation of honey in combination with C. odorata extracts and cimetidine

Honey was combined with aqueous and ethanolic *C. odorata* extracts respectively at (10% w/w) (5 ml kg^{-1}). Cimetidine was also combined with honey at 10 mg/ 1 ml (5 ml kg^{-1}).

Animals

The rats were caged individually in a cylindrical stainless steel cage to avoid coprogaphy. The rats were deprived of food but allowed free access to tap water for 48 hours prior to the experiments. Water was withheld about 18 hours before the experiments. Six rats were assigned to each group and labeled as follows, normal (Group 1); ulcer control (Group 2); pre-treatment with honey alone (Group 3); pre-treatment with honey combined with aqueous *C. odorata* extracts (Group 4); pre-treatment with honey combined with ethanolic *C. odorata* extracts (Group 5); and pre-treatment with honey combined with cimetidine (Group 6). Thirty minutes later, 1 ml of absolute ethanol combined with HCl (0.6 N HCl mixed with equal volume of absolute alcohol) was orally administered to each rat in Group 2, Group 3, Group 4, Group 5 and Group 6 to induce gastric ulceration. Then, 30 minutes later, all the rats were sacrificed by administrating an overdose of diethyl ether then their stomachs were removed and maintained in 10% formalin for further gross and microscopic examination.

Gross and microscopic examination

Each stomach was cut along the greater curvature. The mucosal lesions were traced under the dissecting microscope (x20) with the aid of square-grid eyepiece (1 mm square). The ulcer index (UI) was determined as the sum of gastric lesions for each stomach and the inhibition percentage was expressed as a percentage of the control by the following formula, as earlier described (18):

Inhibition percentage (%)

$= [(UI_{ulcer\ control} - UI_{treated}) / UI_{ulcer\ control}] \times 100$

The stomachs were then trimmed and fixed. Next, the tissues were processed, embedded in paraffin, and subsequently sectioned. The sections were stained with haematoxylin and eosin (H & E) and examined under light microscope at x10 and x40 magnification.

Results

Group 1 (Normal) – Rats administered with distilled water

Rats in this group were administered with distilled water and served as the normal control group. There were no thick black or red lines at the outer stomachs, which were observed before the stomachs were cut opened. Gross examination showed no haemorrhaging and the mucosal rugae was in normal condition. The histology results showed no red blood cells and intact mucosal cells without gastric edema. The submucosa layer appeared to be in normal condition.

Group 2 (Ulcer control) – Gastric lesions produced by absolute ethanol combined with HCl

Oral administration of 1 ml absolute ethanol combined with HCl (mixed equal volume of each) to the rats produced extensive necrosis of the gastric mucosa. Thick black or red lines were visible outside the stomachs, which indicated severe gastric damage. Gross examination showed a large amount of haemorrhagic lesions confined mostly in the gastric corpus, which is the secreting region of the stomach. Histologically, necrosis involved about two-third of the mucosa layer and exfoliation of the mucosal cells was detected. Meanwhile, red blood cells were present in the gastric mucosa and edematous submucosa was discovered as well. Inflammatory exudates were also found around the mucosal layer.

Group 3 – Effects of honey alone on gastric lesions produced by absolute ethanol combined with HCl

Pre-treatment with honey alone before the induction of gastric lesions by absolute ethanol combined with HCl showed modest cytoprotective effect to the gastric mucosa. About half of the stomach showed haemorrhagic condition. Honey inhibition of gastric lesions produced by absolute ethanol combined with HCl was 46.74% (Table 1). Histological examination showed the presence of red blood cells and moderate exfoliation of mucosal epithelial cells. However, the mucosa

Table 1. Tabulated results of gross examination of all oral treatment

Group	Treatment	No. of Rats	Ratio of Treatment to Honey	Dose	Ulcer Index (Mean ± S.E.M)	Inhibition (%)
1	Normal saline (normal)	6	–	5 ml kg^{-1}	9.17 ± 3.11^{a}	–
2	Abs. ethanol + HCl (ulcer control)	6	–	5 ml kg^{-1}	1194.83 ± 121.02^{b}	–
3	Honey alone	6	–	5 ml kg^{-1}	636.33 ± 26.72^{c}	46.74
4	Aqueous extract *C. odorata* + Honey	6	10% w/w	5 ml kg^{-1}	326.50 ± 31.93^{d}	72.67
5	EtOH. extract *C. odorata* + Honey	6	10% w/w	5 ml kg^{-1}	490.83 ± 52.21^{cde}	58.92
6	Cimetidine + Honey	6	10 mg/1 ml	5 ml kg^{-1}	519.17 ± 12.23^{e}	56.55

All values are expressed as means and standard error. Mean with different superscripts are significantly different at ($P < 0.05$).

appeared to be eroded with the presence of exudates. Neutrophils were found around blood vessels of the submucosa.

Group 4 – Effects of honey combined with aqueous extract of C. odorata *on gastric lesions produced by absolute ethanol combined with HCl*

Pre-treatment with honey and aqueous extract of *C. odorata* significantly prevented the formation of gastric lesions produced by absolute ethanol combined with HCl at an inhibition percentage of 72.67%. Gross examination showed mild haemorrhage lesions with the ulcer index of 326.50 ± 31.93 (Table 1). Histological examination showed intact mucosa layers with mild exfoliation of endothelial cells and a slight edematous submucosa was detected. However, the mucosal layer showed moderate haemorrhagic condition with the presence of red blood cells.

Group 5 – Effects of honey combined with ethanol extract of C. odorata *on gastric lesions produced by absolute ethanol combined with HCl*

Pre-treatment with honey combined with ethanol extract of *C. odorata,* grossly showed reduction of 58.92% gastric lesions induced by absolute ethanol combined with HCl. This pre-treatment indicated reliable cytoprotective effects. Histological examination showed fragile and eroded mucosa layers with moderate exfoliation of endothelial cells. In addition, edematous submucosa and red blood cells was detected.

Group 6 – Effect of honey combined with cimetidine on gastric lesions produced by absolute ethanol combined with HCl

Oral administration of cimetidine combined with honey reduced the formation of gastric lesions that was produced by absolute ethanol combined with HCl at inhibition percentage of 56.55%. This treatment showed cytoprotective effects. Histological examination showed intact mucosa layers with barely any exfoliation of endothelial cells. However, moderate edematous submucosa was detected with the appearance of marginated neutrophil around blood vessels and the superficial region of mucosal layer showed broad haemorrhagic condition.

Discussion

By calculating the inhibition percentage of gastric lesions, all the treatments were compared to ulcer control to measure the percentage that each treatment inhibited gastric lesions. All four treatments showed statistical significance when compared to ulcer control. Rats pre-treated with aqueous extract in combination with honey showed the highest inhibition percentage (72.67%) followed by rats pre-treated with alcoholic extract in combination with honey (58.92%), rats pre-treated with cimetidine in

combination with honey (56.55%) and the lowest was for rats pre-treated with honey alone (46.74%).

In this study, absolute ethanol combined with HCl was used as necrotizing agents to induce ulcer in rats. Ethanol and HCl-induced gastric ulcers are commonly used for evaluation of anti-ulcer activity (19). Absolute ethanol and HCl rapidly penetrates the gastric mucosa (20,21), which explains why 30 minutes was sufficient for developing gastric lesions in rats. In this study, oral administration of absolute ethanol combined with HCl produced extensive exfoliation of gastric mucosa cells which caused bleeding and inflammatory exudation. Ethanol causes haemorrhage lesions by inducing endothelin-1 and constricts gastric vasculature, thereby causing stasis in blood flow (22).

Ethanol also incites vascular damage and alters mucosal microvascular permeability (7). It was suggested that depletion of non-protein sulfhydryl concentration and modulation of nitric oxide system are few of the factors contributing to ethanol-induced gastric lesions (6). Furthermore, reduction in glutathione level and production of oxygen-derived free radicals may contribute to ethanol-induced mucosal damage (7).

Subsequently, these factors stated above lead to the release of vasoactive products from mast cells (e.g. histamine), macrophages, polymorphonuclear leukocytes and other blood cells, which may lead to vascular injury, necrosis, and ulcer formation (20). Other roles of ethanol in generating ulcer also involve disturbances in gastric secretion, gastric mucus reduction (19) and causing submucosal edema (1).

In this study, in addition to evaluating the cytoprotective effects of honey alone, the effect of honey when combined with plant extracts and cimetidine were also evaluated. It was suggested that honey acted as vehicle, whereby honey attributed to the cytoprotective effects of *C. odorata* extracts. The same study also claimed that honey when combined with plant extracts, was more effective in its cytoprotective effect than the plant extracts alone (23). In addition, another reason for combining honey at 10% w/w with *C. odorata* extracts was because honey may help to reduce the toxic effect of the plant extract.

Honey alone showed moderate cytoprotective effects in protecting gastric mucosa against ethanol and HCl. The cytoprotection mode of honey may mainly involve reduction in vascular permeability (7) and an increase in gastric mucosal blood flow (6). Inflammatory exudates levels were found to have decreased (24). In addition, the ability of honey to absorb edema, promote epithelialisation and improve the state of nutrition also contribute to the healing process (6,24). Furthermore, honey also possesses antioxidant properties that abolish the increment of endothelial cell permeability (7). This may be the key factor of honey in preventing extensive exfoliation of mucosal cells induced by ethanol and HCl.

C. odorata is a popular herbal remedy in treating wounds, burns and skin infection (13). Although *C. odorata* has not been well established in promoting cytoprotection toward gastric mucosa, many properties of *C. odorata* in wound healing can be applied in elucidating the mode of protection produced by *C. odorata* in this study.

Polysaccharides are general constituents of Asteraceae family, which holds many therapeutic properties. Alginic acid (heterogeneous polysaccharides) was suggested to form gel layer and acts as barrier against excessive pH changes and thus protects the gastric mucosa (25). It is speculated that polysaccharide constituents contribute to the production of cytoprotective effects in *C. odorata*.

The aqueous extracts of *C. odorata* in this study significantly inhibited the action of ethanol in combination with HCl in inducing ulcer. The cytoprotective effect is statistically significant when compared to honey alone, which showed that the cytoprotective effects of aqueous extracts of *C. odorata* combined with honey was not merely due to the honey only. It was observed that exfoliation of gastric mucosa cells was mild and only occurred at the superficial layer. This may be due to the powerful antioxidant (17) and anti-inflammatory (14) properties of *C. odorata*, which must have prevented the decrease in mucosal cells and vascular permeability induced by ethanol and HCl.

The capacity of *C. odorata* to stimulate the expression of many essential proteins (13) such as increasing endogenous prostaglandin may also contribute to decrease in vascular permeability (26). Furthermore, the extracts of *C. odorata* are known to increase proliferation of epithelial cells (17) and may be involved in the healing process of gastric mucosa. The presence of red blood cells was detected and this may be due to enhancement of haemostasis by *C. odorata* extract to stop bleeding (16).

Compared to the aqueous extract of *C. odorata*, the ethanol extract of *C. odorata* only showed modest cytoprotective effects in preventing gastric damage induced by absolute ethanol and HCl. Even though exfoliations of gastric mucosal cells were moderate, inflammatory exudates were found particularly in the

mucosal and submucosa layers, which may explain the fragile and eroded mucosa layers. This may due to a slight increase of vascular and mucosal cells permeability (27). Furthermore, red blood cells were also detected in the mucosal layers and may also be due to the same reason (20).

Even though the ethanolic method of extraction was also used to extract *C. odorata* in this study, heating the plant in water has actually been the traditional Vietnamese method of preparing *C. odorata* extracts. Furthermore, chromatography evaluation indicated that the compounds found in *C. odorata* extracts such as flavonoids and other phenolic compounds are soluble in hot water. Therefore, it was thought that aqueous extraction method was the best way to obtain the constituents of *C. odorata* (16), and this may be the reason why the aqueous extract of *C. odorata* was more effective in inhibiting gastric lesions induced by ethanol and HCl compared to the ethanolic extract of *C. odorata* in this study. However, the difference between aqueous extract of *C. odorata* and ethanolic extracts of *C. odorata* in generating cytoprotective effects was not statistically significant. This was possibly due to the small number of rats used in the study. Furthermore, pre-treatment with ethanolic extract of *C. odorata* combined with honey was not statistically significant compared to pre-treatment with honey alone (Group 3) and neither was it significant compared to pre-treated with cimetidine combined with honey (Group 6).

Histological examination of the group that was pre-treated with cimetidine combined with honey showed a rather intact mucosal layer even though a broad superficial region of mucosa layer appeared haemorrhagic. Cimetidine is well known for its effectiveness in reducing gastric acidity (28) and this may be the reason behind the intact mucosa layer in this group. A study suggested that cimetidine possesses direct cytoprotective effects on the gastric mucosa (29). However, the dose of cimetidine used in that study was higher (300 mg kg^{-1}) compared to the dose used in the present study, 50 mg kg^{-1}. This may explain the haemorrhages at the superficial region of mucosa layer and also the presence of edematous submucosa (27). The pre-treatment of cimetidine combined with honey was statistically significant compared to pre-treatment of honey alone.

Conclusion

In conclusion, honey alone, aqueous and ethanol extracts of *C. odorata* and cimetidine possess cytoprotective properties. Through histological examination, it was speculated that the cytoprotective effects observed in this study include decreased exfoliation of mucosal cells, reduced inflammatory exudates, minimizing mucosal cells and vascular permeability chances.

Furthermore, in this study, there was no statistical significance between aqueous and ethanolic extracts of *C. odorata* in promoting cytoprotective effects. Nevertheless, both extracts of *C. odorata* were able to deliver satisfying cytoprotective effects in reducing gastric mucosal lesions induced by absolute ethanol combined with HCl.

Further investigation of *C. odorata* in inducing cytoprotectiveness needs to be carried out because it might be beneficial in treating a variety of diseases that are related to gastric mucosal injury.

However, for human consumption, further pharmacological tests need to be conducted to determine appropriate doses for humans and to uncover any adverse effects which may arise from administration of *C. odorata.*

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PSEUDOMONAS AERUGINOSA: EPIDEMIOLOGY OF BACTEREMIA AND ANTIMICROBIAL SUSCEPTIBILITY PATTERN IN A TEACHING HOSPITAL IN KUALA LUMPUR

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ABSTRACT: A cross-sectional study of 109 patients with *Pseudomonas aeruginosa* bacteremia from the University of Malaya Medical Centre (UMMC) in the years 2000 and 2001 was conducted to describe epidemiological features, underlying diseases, possible source of infection, early mortality among patients as well as the antibiotic susceptibility pattern of patients' isolates. Further analysis of the 87 patient records that were available revealed that the mean age was 48.5 years (SD ± 25.1). Fifty-two per cent of cases were male and 48% female. Seventy-nine per cent of infections were nosocomially acquired, 33% of bacteremias were polymicrobial, 47% of patients had a continuous bladder drainage catheter (CBD) *in situ*, 33% had a central venous catheter (CVL) present at the time of bacteremia and 30% were ventilated. Sixty-eight per cent of patients had an underlying immunosuppressed state and 26% had undergone surgery involving general anesthesia in the week prior to isolating *P. aeruginosa*. Among the 23 patients with early mortality, 61% were on inappropriate antimicrobials.

Most of the patients' isolates were sensitive to imipenem (86%), ciprofloxacin (81%), ceftazidime (79%), gentamicin (78%) and cefoperazone (77%). Among the community acquired strains, however, there was 100% sensitivity to imipenem, ceftazidime, cefoperazone and ciprofloxacin. *(JUMMEC 2006; 9(1): 14-19)*

KEYWORDS: *Pseudomonas aeruginosa*, bacteremia, antimicrobial susceptibility

Introduction

Pseudomonas aeruginosa bacteremia has become an important cause of mortality and morbidity over the past few decades. Despite the advent of new antimicrobials and improved health standards, mortality ranges from 18-61% (1) which some studies have found is higher than mortality from other gram-negative bacteremias (2). This increased mortality may be reflective of more severe underlying illness or could be related to the greater inherent virulence of the organism (3), or the fact that the organism may develop resistance while the patient is on treatment (4).

P. aeruginosa, a gram-negative bacillus, is generally recognized as an opportunistic and nosocomial pathogen and rarely causes disease in healthy persons (2,3). It is recovered infrequently from the endogenous microbial flora of healthy individuals (2). It is a common pathogen, however, in patients hospitalized for more than a week and predisposing conditions to developing bacteremia include having an underlying immunosuppressed state, admission to intensive care units, respiratory therapy, surgical procedures, the presence of various catheters and antimicrobial therapy (2,3,5). Community-acquired cases have also increased and this may be related in part to the prevalence of HIV infection and reports that in HIV infected patients, *P. aeruginosa* bacteremia may be community-acquired (6).

There have not been any epidemiological studies on *P. aeruginosa* bacteremia in Malaysia. The objectives of this study were to describe the epidemiologic features, underlying diseases, possible source of infection, percentage of early mortality and the antimicrobial

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susceptibility pattern of isolates in patients with *P. aeruginosa* bacteremia at a tertiary level teaching hospital in Malaysia in the years 2000 and 2001.

Material and Methods

Patients

All 109 patients with *P. aeruginosa* bacteremia in the years 2000 and 2001 were identified from the computerized microbiology records of the Microbiology laboratory of the University of Malaya Medical Centre (UMMC), an 844-bed major teaching hospital in Kuala Lumpur, Malaysia. There were 45 cases in the year 2000 and 64 cases in the year 2001. However, only 87 patient records were available for further analysis.

Inclusion criteria for *P. aeruginosa* bacteremia was at least one positive blood culture from a patient with suspected bacteremia. Cases with polymicrobial bacteremia involving *P. aeruginosa* were also included in this study. The patients' demographic information as well as information regarding therapy with steroids, cytotoxic drugs, presence of hematological or other malignancies, other immunosuppressed states like burns and post-splenectomy, diabetes mellitus, central venous lines (CVL), continuous bladder drainage catheter (CBD) and mechanical ventilation was recorded. Patients who had undergone surgery in the week prior to the isolation of *P. aeruginosa* from the blood were also identified.

Microbiology

The microbiology data collected included the antimicrobial sensitivity pattern of all 109 bacteremic *P. aeruginosa* isolates as well as the types of organisms isolated in the polymicrobial cases. If the organism was isolated from another site of the body within a week prior to the positive blood culture, this was also recorded.

Blood cultures were processed by the Bactec 9240 system (Becton-Dickinson Microbiology System, USA). *P. aeruginosa* was identified by conventional bacteriological methods or by the API 20NE system (bioMérieux, France). Antibiotic susceptibility testing by disc diffusion was in accordance with the National Committee for Clinical Laboratory Standards (NCCLS) (7,8).

Definitions

Nosocomial infection was defined as a positive blood culture taken 48 hours after admission with no evidence of *Pseudomonas aeruginosa* infection at the time of admission. The bacteremia was considered to be community-acquired if *P. aeruginosa* was isolated within 48 hours of hospital admission and the patient had not been admitted in the previous two weeks (1). Patients were classified as immunosuppressed if they were on cytotoxics or steroids, had underlying malignancy, diabetes, HIV infection, systemic lupus erythematosus, burns, or had been splenectomized. Diabetes as an underlying factor was also analyzed separately.

Polymicrobial bacteremia was defined as the isolation of other organisms in addition to *P. aeruginosa* from the blood culture. If a specimen from any site of the body grew *P. aeruginosa* within a week prior to isolating the organism from the blood, it was considered a possible portal of entry; otherwise, the source of bacteremia was considered unknown. Early mortality was defined as death occurring within 72 hours of isolating the organism from a blood culture and antimicrobial therapy at the time of bacteremia in these cases was considered appropriate if the strain of *Pseudomonas aeruginosa* isolated was sensitive to any of the antimicrobials given to the patient and if the patient received adequate dosage of that antibiotic for at least 24 hours prior to death.

Results

Demography

Table 1 shows the characteristics of the study subjects. The mean age of the 87 patients was 48.5 years (SD ± 25.1; range: 13 days old to 92 years). Fifty-two per cent

Table 1. Characteristics of study subjects

Risk factors	No. of patients (%) (Total patients n=87)
Age (Year)	
0 – 12	11 (13%)
13 – 29	10 (11%)
30 – 49	17 (20%)
50 – 69	33 (38%)
> 70	16 (18%)
Sex	
Male	45 (52%)
Female	42 (48%)
Ward type	
Intensive care units	20 (23%)
Surgical	22 (25%)
Hematological	19 (22%)
Adult medical	15 (17%)
General paediatric	5 (6%)
Gynaecology	4 (5%)
Renal	2 (2%)

of patients were male and 48% were female. Twenty patients (23%) had been in an ICU at the time of bacteremia, 22 (25%) were from the surgical wards, 15 (17%) were from the adult medical ward, 5 (6%) were from the general paediatric wards, 19 (22%) from the haematology wards, 4 (5%) were from the gynaecology ward, and two patients (2%) were from the renal wards.

Underlying disease associated with P. aeruginosa *bacteremia*

Fifty-nine patients (68%) were classified as immunosuppressed at the time of bacteremia (Table 2). Twenty patients (23%) had underlying haematological malignancy, 22 (25%) had other non-haematological malignancies, 11 (13%) were on steroids, three (3%) had burns, three (3%) had systemic lupus erythematosus, two (2%) had been splenectomized and two (2%) had HIV infection. Twelve patients (14%) were diabetic.

Forty-one patients (47%) had a CBD *in situ*, 29 (33%) had a CVL present at the time of bacteremia and 26 patients (30%) were on ventilator. Twelve patients (14%) had undergone surgery involving general anesthesia in the week prior to isolating *P. aeruginosa* from the blood. Six patients (7%) had a tracheostomy and one patient had a ventriculo-peritoneal shunt.

Source of infection

Among the 87 bacteremic cases, sixty-nine (79%) were nosocomial in origin whilst 16 (18%) were community-acquired (Table 2). In two patients (2%), the information available was insufficient to determine a nosocomial or community origin. Among the patients with community-acquired bacteremia, nine (56%) had underlying carcinoma, haematological malignancy, or had undergone bone marrow transplant. The remaining seven patients had the following underlying conditions: polycystic kidneys and urinary tract infection with *P. aeruginosa,* HIV infection, diabetes with gangrene of the foot, liver cirrhosis, burns, upper gastrointestinal tract bleeding with polymicrobial bacteremia, and one was an infant with a prior history of being admitted to the special care nursery a month earlier.

The urinary tract was possibly the commonest identified site of entry (11%); this was followed by the respiratory tract (10%) and intravenous catheters (6%) (Table 2). Thirteen per cent of patients also had various wound swabs and drainage fluids growing *P. aeruginosa* in the week prior to isolation of the organism. However, it was not possible to determine accurately where the swabs and fluids had been taken from due to the retrospective nature of the study. In 62% of cases the site of entry was unknown.

Early mortality

Early mortality occurred in 26% (23/87 patients), and the *P. aeruginosa* bacteremia is likely to have been a contributing factor. Table 2 shows patient characteristics and underlying conditions in relation to early mortality.

Of the 23 patients with early mortality, 70% were male, 70% had monomicrobial bacteremia, 61% had nosocomial bacteremia, 61% were on inappropriate antibiotics, 61% had an underlying immunosuppressed state and 52% had a CBD catheter.

Microbiology

Twenty-nine cases (33%) were polymicrobial with various other organisms isolated in addition to *P. aeruginosa* (Table 3). Gram-negative bacilli and gram-positive cocci were isolated from 14 and 9 specimens respectively. Six specimens yielded both gram-negative bacilli and gram-positive cocci in addition to *P. aeruginosa*. The commonest organism isolated was *Staphylococcus aureus*, followed by *Enterococcus* spp. More than half (52%) of the polymicrobial bacteremia cases were from intensive care unit (ICU).

Antimicrobial sensitivity of isolates

All isolates had been tested for sensitivity against ceftazidime, cefoperazone, gentamicin, ciprofloxacin and imipenem. The majority of isolates (86%) were sensitive to imipenem, 81% were sensitive to ciprofloxacin; this was followed by ceftazidime (79%), gentamicin (78%) and cefoperazone (77%) (Table 4). Among the community-acquired strains, however, there was 100% sensitivity to imipenem, ceftazidime, cefoperazone and ciprofloxacin.

There were three strains resistant to piperacillin but sensitive to piperacillin/tazobactam, two strains were sensitive to imipenem but resistant to meropenem and another two were resistant to imipenem but sensitive to meropenem. Among the aminoglycosides, there were 11 isolates resistant to gentamicin but sensitive to amikacin, but none were sensitive to gentamicin and resistant to amikacin. There were four multi-resistant strains which were only sensitive to polymixin B. Two of these strains came from patients in the ICU, and one each from the adult surgical and medical wards.

Table 2. Patient characteristics and underlying conditions in relation to early mortality

Patient characteristic/ underlying condition	No. of patients (%) (Total patients n=87)	No. of patients dying within 72 hours (%) (Total patients n=23)	No. of patients dying in 72 hours/ total patients in the group (% total in the group)
Age (Year)			
0 – 12	11 (13%)	5 (22%)	5/11 (45%)
13 – 29	10 (11%)	2 (9%)	2/10 (20%)
30 – 49	17 (20%)	2 (9%)	2/17 (12%)
50 – 69	33 (38%)	10 (43%)	10/33 (30%)
> 70	16 (18%)	4 (17%)	4/16 (25%)
Sex			
Male	45 (52%)	16 (70%)	16/45 (36%)
Female	42 (48%)	7 (30%)	7/42 (17%)
Admission to an intensive care unit	20 (23%)	8 (35%)	8/20 (40%)
Immunosuppressed state	59 (68%)	14 (61%)	14/54 (24%)
All malignancies	42 (48%)	8 (35%)	8/42 (19%)
– Haematological malignancies	20 (23%)	7 (30%)	7/20 (35%)
– Other malignancies (bowel cancer, gynaecological, etc.)	22 (25%)	4 (17%)	4/22 (18%)
Diabetic patient	12 (14%)	2 (9%)	2/12 (17%)
Presence of CBD	41(47%)	12 (52%)	12/41(29%)
Presence of CVL	29 (33%)	6 (26%)	6/29 (21%)
On ventilator	26 (30%)	8 (35%)	7/26 (27%)
Recent surgery	12 (14%)	2 (9%)	2/12 (17%)
Source of bacteremia			
– Nosocomial	69 (79%)	16 (61%)	16/69 (23%)
– Community*	16 (22%)	7 (39%)	7/16 (45%)
Possible route of entry			
Respiratory tract	9 (10%)	2 (9%)	2/9 (22%)
Urinary tract	10 (11%)	2 (9%)	2/10 (20%)
Central venous catheters	5 (6%)	1 (4%)	1/5 (20%)
Others (swabs/drainage fluids)	11 (13%)	2 (9%)	2/11 (18%)
Type of bacteremia			
Monomicrobial	58 (67%)	16 (70%)	16/58 (28%)
Polymicrobial	29 (33%)	7 (30%)	7/29 (24%)
Treatment			
Appropriate	–	9 (39%)	–
Inappropriate	–	14 (61%)	–

* Of the community-acquired cases, nine had underlying malignancies or had undergone bone marrow transplant. The remaining seven had the following underlying conditions: polycystic kidneys with a urinary tract infection (*P. aeruginosa),* diabetes with gangrene of the foot, HIV infection, liver cirrhosis, burns, upper gastrointestinal tract (GIT) bleeding with polymicrobial bacteremia, and a history of having being admitted to the special care nursery a month earlier.

Table 3. Organisms isolated in polymicrobial cases involving *P. aeruginosa*

Microorganisms	No. of isolates
Gram-positive cocci	
Staphylococcus aureus (three isolates were methicillin resistant *S. aureus*)	6
Enterococcus spp.	5
Staphylococcus epidermidis	3
Gram-negative rods	
E. coli	4
Stenotrophomonas maltophilia	2
Enterobacter spp.	3
Klebsiella spp.	4
Acinetobacter spp.	4
Pseudomonas spp.	1
Yeast	1

Discussion

The majority of patients with *P. aeruginosa* bacteremia had an underlying immunosuppressed state or some device present that predisposed them to the development of infection, this being similar to findings in other published reports (1,3). The patients were mainly distributed among the intensive care units, surgical and haematological wards, whereas a predominance of patients from the general surgical and transplant services were found (6).

Although most of the cases (79%) were nosocomial infections, community-acquired cases were also seen (18%) and these findings were similar to a recent study (9). Research has shown that only 12% (1) of cases were community-acquired whereas a rate of 40% was reported (6). This was higher than their earlier study of 17% and the increase in community-acquired cases was partially attributed to the prevalence of HIV infection as in seven out of 11 episodes of *P. aeruginosa* bacteremia in these patients, the bacteremia was community-acquired (6). In our study, we had only one patient with underlying HIV infection among the community-acquired cases but most patients had some other underlying immunosuppressed state or predisposing factor.

Early mortality in our study was seen in 26.3% of patients. In a study of *Pseudomonas* septicemia in cancer patients 33% of patients died in the first 24 hours (10). In another study, 21 out of 23 patients had cancer, and the median period of survival from the positive blood culture was four days (11).

Polymicrobial bacteremia in this study was seen in 33% of the bacteremic cases, which was much higher than the 17% reported (12). Fifty-two per cent of these cultures were from ICU patients. However, contamination may have been responsible for some of the cases. Patients with polymicrobial bacteremia were clinically worse and had a higher mortality rate compared to patients with monomicrobial *P. aeruginosa* bacteremia (12). In our study, however, 70% of patients with early mortality had monomicrobial bacteremia with *P. aeruginosa*. The most common organism isolated along with *P. aeruginosa* was *Enterococcus* spp. (12), whereas in our study, *Staphylococcus aureus* was the commonest organism isolated, followed by *Enterococcus* spp.

It was not possible to determine with certainty the source of bacteremia in our patients, but 47% of the patients had a CBD catheter *in situ* and among those in whom a presumed source of infection was found, a urinary portal of entry was the commonest (11%), followed by the respiratory tract (10%). Studies have found that the respiratory tract was the commonest source for *P. aeruginosa* septicemia (6).

Table 4. Sensitivity of *P. aeruginosa* to antimicrobials

	Antibiotic									
	CAZ	CFP	GM	AN	CIP	IPM	MEM*	PIP	P/T*	SCF
Percentage sensitive	79	77	78	91	81	86	76	80	100	81
(No. tested)	(109)	(109)	(109)	(100)	(109)	(109)	(49)	(104)	(25)	(95)

Key:

S = sensitive

CAZ = ceftazidime, CFP = cefoperazone, GM = gentamicin, AN = amikacin, CIP = ciprofloxacin, IPM = imipenem, MEM = meropenem, PIP = piperacillin, P/T = piperacillin/tazobactam, SCF = cefoperazone/sulbactam

** Number of strains tested against these antimicrobials were few as they were not part of the routine testing panel in our laboratory at the time of this study. Isolates were only tested against these antimicrobials if multi-resistant or if specifically requested for by the clinicians.*

Conclusion

This study has highlighted the common epidemiological features of patients with *P. aeruginosa* bacteremia in our hospital, but being retrospective and not case controlled, firm statistical conclusions could not be made. As only 87 of the 109 patients' records were available for analysis, any bias in results cannot be excluded.

Most of our isolates were sensitive to imipenem, ciprofloxacin, ceftazidime, gentamicin and cefoperazone and for community-acquired isolates all were sensitive to imipenem, ceftazidime, cefoperazone, and ciprofloxacin. Therefore, if a *P. aeruginosa* septicemia was suspected or confirmed in a patient in our hospital, these antimicrobials would probably be effective as empirical therapy while awaiting results of sensitivity. Although not all isolates were tested against amikacin, among those tested, 91% were found to be sensitive. Four isolates were found to be resistant to all antibiotics except polymyxin B. Antibiotic selection for treatment of infections caused by *P. aeruginosa* is often problematic (4). In our study, 61% of patients with early mortality had been on inappropriate empirical antimicrobials. There have been conflicting reports about mortality in relation to whether patients had received appropriate or inappropriate antibiotics, with several studies failing to show a difference (1,13,14) and others showing a decrease in mortality when appropriate antibiotics were used (15,16,17,18).

Nonetheless, it does seem prudent to start empirical antimicrobials that are likely to be effective against *P. aeruginosa* if it is thought to be a likely pathogen, particularly, when dealing with immunosuppressed patients.

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BODY FAT COMPARISON BETWEEN BASKETBALL AND NETBALL PLAYERS IN MALAYSIA

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ABSTRACT: The aim of the study was to compare the body fat percentages between Malaysian national women basketball players and netball players. Both basketball and netball players were elite players who represented Malaysia in the 1997 Southeast Asia Games in Jakarta, Indonesia and the 1998 Commonwealth Games in Kuala Lumpur. The percentage of body fat was determined by means of skinfold measurement at seven different locations. Results of the findings showed that overall, the basketball players had higher percentages of body fat than netball players. The average percentages of body fat of basketball and netball players were 19.68 ± 4.93% and 18.93 ± 4.41%, respectively. Both Malaysian national basketball and netball players' average percentage of body fat were found to be higher than the ideal average percentage of body fat range between 10-16% for female athletes in elite team sports. The players in the defence position in basketball were found to have the highest percentage of body fat (23.00%), followed by centre position players (21.62%) and attack position players (15.10%). These results differed from netball players' in similar playing positions. Among the netball players, the defence position players had the highest percentage of body fat (21.00%), followed by attack position players (18.63%), and centre position players (16.57%). *(JUMMEC 2006; 9(1): 20-22)*

KEYWORDS: Body fat, netball players, basketball players, playing position

Introduction

Basketball and netball are among the popular contact sports in Malaysia. Netball evolved from a common progenitor with basketball, and therefore, there are similarities between the games. According to a study carried out (1,2), female athletes in elite team sports such as basketball and netball need a body fat percentage of 10% to 16% or skinfold value of 70-90 mm (averaged from seven locations) to perform well or to achieve their full playing potential. They reported that players with body fat percentages of 12% to 16% had better overall physical fitness, better movement and tired less easily compared to players who were reported to have skinfold values exceeding the ideal level. Body fat in excess of 25% would limit the players' movements. They would also be tired faster from lugging the extra weight around. Moreover, more oxygen would be needed to catabolize the fat for the extra energy required (3). All these would lower their level of play. Hence, the purpose of this study is to compare the body fat percentage among elite basketball and netball players in Malaysia, and to identify whether the body fat value was in line with the suggestion given (1,2).

Methods and Procedures

Subjects

Twenty-three physically active elite Malaysian basketball (N=12) and netball (N=11) players were chosen for this study. The basketball and netball players were elite players who represented Malaysia in the 1997 Southeast Asia Games in Jakarta, Indonesia and the 1998 Commonwealth Games in Kuala Lumpur, respectively. Players from both teams were elite players as they were the best national teams in Malaysia, and participated in the highest level of competition in their respective games. The subjects were divided into three categories, i.e., defender/guard, centre, and attacker/

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forward. The physical characteristics of the subjects for the games are shown in Table 1.

Procedure and Instrumentation

The study was carried out at the Malaysian National Sports Institute, Bukit Jalil. A trained physiologist, who was working with the institute, took these measurements. According to Tothill and Stewart, measurements taken by trained personnel should be fairly reliable (4). Seven locations were pinched – chest, mid-axilla, subscapular, triceps, suprailiac, navel, and thigh – using a Harpenden caliper. Seven skinfold location sites were chosen because the more locations taken, the more accurate the results would be (5). Furthermore, more skinfold sites taken were also reported to have higher correlation (r=0.85) with Hydrostatic Weighing (6,7). The calculation of body fat content was based on the formula (6).

Statistical Analysis

The overall and based on playing positions body fat contents were reported in percentages and the body fat comparison between both teams were done directly based on the percentages (8). Besides that, both the body fat percentage values obtained were also used to determine whether they were in line with the suggestion given (1,2).

Results

A mean body fat percentage of 19.68 ± 4.93% was reported among the elite basketball players. The body fat range in this study was 10.40% to 26.20% (Table 2). The defence women basketball players had the highest body fat percentage, followed by the centre and attack players. The body fat percentages among the basketball players based on the above playing positions were 23.00 ± 3.39% (defence), 21.62 ± 3.91 (centre), and 15.10 ± 4.12% (attack), respectively (Table 3). Meanwhile, the netball players had a mean of 18.93 ± 4.41% body fat. The body fat range was from 13.20% to 25.70% (Table 2). Defence netball players had the highest body fat percentage of 21.00 ± 4.89%, followed by attack 18.63 ± 5.40%, and centre 16.57 ± 5.40% position players (Table 3).

Table 1. Mean values of physical characteristics for the basketball and netball players

Teams	N	Age (years)		Height (cm)		Body Mass (kg)	
		Mean	SD	Mean	SD	Mean	SD
Basketball	12	22.75	2.67	171.71	5.45	63.88	6.46
Netball	11	23.91	3.36	168.70	6.74	61.34	7.92

Table 2. Body fat percentages (%) among basketball and netball players

Basketball Players	Body Fat (%)	Netball players	Body Fat (%)
1	18.30	1	21.50
2	10.40	2	20.90
3	18.80	3	17.30
4	12.90	4	14.80
5	22.00	5	13.20
6	16.60	6	13.70
7	19.00	7	22.80
8	26.20	8	19.50
9	26.10	9	24.00
10	19.80	10	25.70
11	25.40	11	14.80
12	20.60		
Body Fat Range	10.40 – 26.20%		13.20 – 25.70%
Mean and SD	19.68 ± 4.93		18.93 ± 4.41

Table 3. Mean body fat percentage (%) based on playing position

Teams	Positions						Overall	
	Attack	SD	Centre	SD	Defense	SD	Mean	SD
Basketball	15.10	4.12	21.62	3.91	23.00	3.39	19.68	4.93
Netball	18.63	3.15	16.57	5.40	21.00	4.89	18.93	4.41

Discussion

The overall body fat percentages of 19.86% and 18.93% among the Malaysian basketball and netball players were found to be higher compared to the ideal norm of 10% to 16% (1). However, there were two basketball players and four netball players who had body fat percentages within the 10% to 16% range. The range of percentage of body fat among the Malaysian basketball and netball players is between 10.40% to 26.20% and 13.20% to 25.70%, respectively (Table 2). Results of this study also showed that there were three basketball players and one netball player with body fat percentages exceeding 25%. According to research (1), body fat in excess of 25% would limit the players' movements. They would also become tired faster from lugging the extra weight around. Moreover, more oxygen would be needed to catabolize the fat for the extra energy required (3). All these would lower their level of playing performance and prevent them from playing to their full potential (2). Meanwhile, for playing position, only attack basketball players were found to have the most suitable body fat percentage for a good basketball player. These players had mean body fat percentage of 15.10% (Table 3).

Conclusion

The Malaysian elite women basketball and netball players were found to have higher body fat percentages compared to the elite basketball players' norm of 10% to 16% (1). Of all the subjects, only two basketball players and four netball players were found to have suitable body fat percentages required to be a good basketball or netball player. Most of the basketball and netball players were found to have acceptable body fat percentage, i.e., body fat less than 25%. However, three basketball players and one netball player had body fat percentages exceeding the 25% (Table 2), which is considered high for elite national players (9). An above average body fat was reported to have an impact on running speed, jumping ability and endurance performance (2).

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RISPERIDONE AND OLANZAPNE IN-PATIENT UTILIZATION IN THE UNIVERSITY OF MALAYA MEDICAL CENTRE, KUALA LUMPUR

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ABSTRACT: The objective of this study was to compare in-patient drug use patterns, costs, and outcomes associated with risperidone or olanzapine in a naturalistic clinical setting. Retrospective chart reviews of 92 patients with psychotic disorders were conducted at the University of Malaya Medical Centre (UMMC). Data was collected from patients who were hospitalized and for whom risperidone or olanzapine was the drug of first choice for long-term pharmacologic treatment.

Proportion of patients for whom efficacy of the studied treatment could be established (as rated by the treating physician) was higher, but not significantly, with risperidone compared to olanzapine (p = 0.46). The average dose of the studied medication was 2.9 ± 1.0 mg/day for risperidone and 9.7 ± 2.4 mg/day for olanzapine. The total cost was significantly higher (p < 0.0001) for olanzapine (RM140.40; 95% CI: 108.4–181.9) compared to risperidone (RM50.80, 95% CI: 39.5–65.3). The daily cost was also significantly higher for olanzapine (RM19.16; 95% CI: 17.72–20.72) compared to risperidone (RM4.95; 95% CI: 4.46–5.51, p < 0.0001). Analysis of responders showed significantly higher daily and total costs of treatment with olanzapine compared to risperidone. These preliminary data suggest that treatment with risperidone may be more cost-effective than treatment with olanzapine. However, a longer duration of study and more data is needed before a proper conclusion on cost-effectiveness is made. *(JUMMEC 2006; 9(1): 23-29)*

KEYWORDS: antipsychotic, outcome

Introduction

The novel or atypical anti-psychotic medications introduced over the last decade represent a significant step forward in pharmacotherapy. Risperidone (*Risperdal*®) and olanzapine (*Zyprexa*®) are novel anti-psychotic agents belonging to the new class of atypical anti-psychotics that was first defined by the introduction of clozapine. The exact mechanism of action of both drugs has not been fully elucidated. It may involve antagonism at serotonin type 2 (and type 3 and 6 for olanzapine) and dopamine receptors (1).

While conventional anti-psychotics effectively reduce psychotic symptoms, they often induce extrapyramidal side effects and tardive dyskinesia. The atypical agents are generally free of these unwanted effects and generally have a more favourable adverse-effect profile than conventional anti-psychotics (2,3). Moreover, in addition to effectively treating positive psychotic symptoms, atypical agents are often helpful for patients unresponsive to conventional agents and may be more effective for negative symptoms and cognitive dysfunction. These characteristics improve drug compliance and yield a decline in the number of relapses and the need of hospitalization (4,5).

While cost-effectiveness of atypical anti-psychotics versus the conventional drugs has been extensively documented and demonstrated, the relative cost-effectiveness of the atypical anti-psychotics among each other has not yet been widely investigated. A study from North America suggests that olanzapine is associated with higher treatment costs (on average twice as costly), while this is not compensated for by any clinical advantage (6). The present study was a single centre, retrospective comparative study. The objective of this study was to compare the drug usage pattern, the costs and outcomes associated with

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treatment of psychotic disorders with either risperidone or olanzapine within a single hospital setting in Malaysia.

Methods

Study outline

Data was collected at the University of Malaya Medical Centre (Malaysia) from patients who had been hospitalized and for whom risperidone or olanzapine was the first intended drug for long-term pharmacological treatment after admission.

The total number of patients required within each treatment group was 33. The most recent admissions were systematically checked in reverse chronological order and patients were included if the following criteria were met:

1. Risperidone or olanzapine was the first intented drug for long-term treatment;
2. Patient was not older than 65 years; and
3. The patient was discharged from the hospital before 120 days.

The most recent patients treated by olanzapine and the most recent patients treated by risperidone were selected. Data regarding demography, history of psychiatric illness (diagnosis, number of previous hospitalizations), diagnosis upon admission, hospitalization information (length of hospital stay, discharge status), medication history, usage pattern of drugs used over the length of stay in hospital, dose details of the study treatments (risperidone and olanzapine, details of other neuroleptics or other relevant concomitant medications, treatment efficacy (efficacy assessment: effective, ineffective or partially effective as rated by the treating physician) and side effects related to neuroleptics were collected.

Primary parameters (outcome measures)

The primary parameters were the average daily costs of the drugs (*Risperidone*/*Olanzapine*) under study.

Secondary parameters (outcome measures)

The secondary parameters were the average daily dose and cost of studied treatments (risperidone or olanzapine), the time to discharge, the proportion of patients who discontinued treatment and switched from risperidone or olanzapine to other anti-psychotic treatment, the treatment efficacy as rated by the treating physician, the number of days before efficacy was established and the side effect profile.

Patient populations

Two populations were considered:

1. The intention-to-treat (ITT) populations, consisting of patients who had been treated with the treatment to which they were assigned;
2. The responders, defined as patients whose treatment was judged as effective by the treating physician and who did not discontinue the treatment for any reason except if the treatment was no longer deemed necessary.

Data analysis

Dosage parameters were analyzed by descriptive methods (mean, standard deviation, median, minimum and maximum) without statistical comparison between risperidone and olanzapine. Costs between treatments were analyzed by descriptive statistics and compared by using t-test on the log-transformed data because log-normal distribution fits the data better than the normal distribution. The mean cost was summarized by the geometric mean and its 95% confidence interval.

Proportions of patients were compared between treatments using Fisher's exact test. Number of days before efficacy was established, was compared using the non-parametric Mann-Whitney rank test.

The time to event parameters (e.g., time to onset of efficacy, time to discharge) was also analyzed using survival analysis methods to take into consideration censored data (patient for whom efficacy was not reached). The Kaplan-Meier product-limit estimate of the survival function was calculated and the comparison between treatments was carried out using non-parametric tests (Generalized Wilcoxon test and log-rank test).

Ethics

The study was approved by the University of Malaya Medical Centre ethics committee. Consent was obtained from patients prior to data collection.

Results

Ninety-two patients (Risperidone: 43, Olanzapine: 49) were part of the study. There were 67 responders (Risperidone: 35, Olanzapine: 32). Among the 25 non-responders, the study treatment was rated as ineffective by the physician in 12 patients, the treatment was rated as partially effective in ten others, and the efficacy was not assessed in three patients.

Demography and patient's profile are summarized in Table 1. Patients treated with risperidone were significantly older at admission than those treated by olanzapine (median: 35.9 vs. 29.5 years, respectively, $p = 0.02$). The age at onset of first symptoms was higher in the risperidone group than in the olanzapine group (median: 27.3 vs. 25.5 years, respectively). However, the difference was not statistically significant ($p = 0.11$). The proportion of females and males was similar in both groups ($p = 0.40$). The groups differed significantly regarding the pattern of diagnosis ($p = 0.002$). There were proportionally more patients with diagnosis other than schizophrenia in the olanzapine group (bipolar: 33%; other diagnosis: 31%) than in the risperidone group (bipolar: 7%; other diagnosis: 16%).

Table 1. Demography and patient's profile (ITT patients)

Parameter	Risperidone (N=43)	Olanzapine (N=49)	*p*
Age at onset of first symptoms (y)	31.3 ± 14.9	27.2 ± 9.0	0.11
Age at admission (y)	39.1 ± 16.4	32.2 ± 11.3	0.02
Gender Males	18 (43%)	26 (53%)	0.40
Females	24 (57%)	23 (47%)	
Diagnosis:			0.002
– Catatonic schizophrenia	1 (2%)	0	
– Disorganised schizophrenia	1 (2%)	0	
– Paranoid schizophrenia	23 (53%)	14 (29%)	
– Undifferentiated schizophrenia	8 (19%)	4 (8%)	
– Bipolar	3 (7%)	16 (33%)	
– Other diagnosis	7 (16%)	15 (31%)	
Previous hospitalization	22 (51%)	27 (55%)	0.83
Number of previous hospitalizations:			0.45
0	21 (49%)	22 (45%)	
1 – 5	19 (44%)	25 (51%)	
6 – 10	3 (7%)	2 (4%)	
History of medication available	26 (60%)	27 (55%)	0.68
Use of anti-psychotics during the previous year (‡)	26 (100%)	27 (100%)	–
Number of previous anti-psychotics: (‡)			0.21
0	0	0	
1	12 (46%)	9 (33%)	
2	13 (50%)	14 (52%)	
3	1 (4%)	4 (15%)	
Number of patients who discontinued previous anti-psychotics: (§)			
– for any reason	26 (100%)	26 (96%)	>0.99
– for lack of efficacy	17 (65%)	19 (70%)	0.77
– for side effects	12 (46%)	12 (44%)	>0.99
– for other reason(s)	4 (15%)	5 (19%)	>0.99
Number of previous anti-psychotics discontinued: (‡)			0.7
0	0	1 (4%)	
1	12 (46%)	11 (41%)	
2	13 (50%)	11 (41%)	
3	1 (4%)	4 (15%)	

Values are numbers of patients (%) except for age: mean ± SD

(‡): Percentages are calculated using the patients with available history of medications as denominator (N=26 and 27 patients for risperidone and olanzapine, respectively);

(§): Percentages are calculated using the patients who took previous anti-psychotics (N=26 and 27 patients for risperidone and olanzapine, respectively).

The proportion of patients with previous hospitalizations was similar in both groups (p = 0.83). The number of previous hospitalizations exceeded five times in 7% of the risperidone patients and in 4% of the olanzapine patients. Of the patients with available history of medication, there were 60% in the risperidone group and 55% in the olanzapine group (p = 0.68). Of these patients, all in both groups had used anti-psychotics in the previous year. The number of previous anti-psychotics used by patients was similar in both groups (p = 0.21). The proportion of patients who discontinued previous anti-psychotics was also similar in both groups. Reasons for discontinuation were lack of efficacy in 36 patients (Risperidone: 17; Olanzapine: 19), side effects in 24 patients (12 in each group), and other reasons in nine patients (Risperidone: 4; Olanzapine: 5). Based on the list of previous anti-psychotics, only one olanzapine patient was already treated with the medication under study when admitted at the hospital.

Main parameters of interest are summarized in the Table 2. Proportion of patients for whom efficacy of the treatment could be established (as rated by the treating physician) was higher with risperidone (81%) than with olanzapine (70%). However, the difference was not statistically significant (p = 0.46). The number of days before treatment efficacy was established was similar in both groups (median: 6.0 days for both treatments, p = 0.60). The difference between groups in the curve of the time to efficacy distribution function (including censored observations) was not statistically significant ($p \geq 0.59$, Figure 1).

The average daily dose was 2.9 mg/day for risperidone patients and 9.7 mg/day for olanzapine patients. The study treatment duration was slightly longer in the risperidone group than in the olanzapine group (10.2 vs. 7.3 days, respectively). However, the difference reached a statistical tendency (p = 0.07). The average daily cost of the medication was significantly higher for olanzapine than for risperidone (Ringgit Malaysia (RM) 19.16 vs. RM4.95, respectively, $p < 0.0001$). The total cost of treatment was significantly higher for olanzapine than for risperidone (RM140.4 vs. RM50.8, respectively, $p < 0.0001$). When considering the responders only (Table 3), the results also showed significantly higher daily and total costs of treatment with olanzapine compared to risperidone.

Utilization of other neuroleptics and other relevant concomitant medications (anti-epileptics, anti-Parkinson, anxiolytics, hypnotics and sedatives, and anti-histamines) is summarized in Table 4. The proportion of patients who took at least one other neuroleptic or one other relevant concomitant medications (started at any time)

Table 2. Main parameters of interest (ITT patients)

Parameter	Risperidone (N=43)	Olanzapine (N=49)	p
Number of patients	43 (100%)	49 (100%)	–
Number of patients with effective treatment (§)	35 (81%)	32 (70%)	0.46
Number of days before efficacy was established (‡)	6 (1–21)	6 (2–14)	0.60
Number of patients who discontinued the treatment	0	1 (2%)	>0.99
Average daily dose (mg)	2.9 ± 1.0	9.7 ± 2.4	
Study treatment duration (days)	10.2 (8.4; 12.5)	7.3 (5.9; 9.1)	0.07
Total cost (RM) of treatment drug	**50.8 (39.5; 65.3)**	**140.4 (108.4; 181.9)**	**<0.0001**
Daily cost (RM) of treatment drug	**4.95 (4.46; 5.51)**	**19.16 (17.72; 20.72)**	**<0.0001**

Values are patient numbers (%) except for dose: mean ± SD, number of days before efficacy: median (minimum – maximum) and costs and study treatment duration: geometric means (95% confidence interval).
(§): Efficacy of three olanzapine patients was not assessed (N=43 for risperidone, N=46 for olanzapine);
(‡): Statistics are calculated on the patients whose efficacy was established (N=35 for risperidone, N=32 for olanzapine).
US$ = RM3.80

Table 3. Main parameters for responders

Parameter	Risperidone (N=35)	Olanzapine (N=32)	p
Average daily dose (mg)	2.9 ± 0.9	9.5 ± 1.9	
Study treatment duration (days)	11.3 (9.1; 14.1)	10.2 (8.4; 12.5)	0.58
Total cost (RM) of treatment drug	**56.7 (43.8; 73.5)**	**195.2 (150.5; 253.2)**	**<0.0001**
Daily cost (RM) of treatment drug	**5.01 (4.50; 5.58)**	**19.09 (17.48; 20.85)**	**<0.0001**

Values are geometric means (95% confidence interval) except for dose: mean ± SD.

Table 4. Use of other neuroleptics and other concomitant medications

Parameter	Risperidone (N=43)	Olanzapine (N=49)	*p(*)*
Number of patients who took other neuroleptics			
Pre-existing of Ris./Ola. treatment	25 (58%)	30 (61%)	0.83
Since initiation of Ris./Ola. treatment	7 (16%)	4 (8%)	0.34
After initiation of Ris./Ola. treatment	1 (2%)	1 (2%)	>0.99
Number of patients who took other relevant concomitant medications			
Pre-existing of Ris./Ola. treatment	21 (49%)	19 (39%)	0.40
Since initiation of Ris./Ola. treatment	8 (19%)	10 (20%)	>0.99
After initiation of Ris./Ola. treatment	4 (9%)	6 (12%)	0.75
Number of patients who took other neuroleptics or concomitant medications			
Pre-existing of Ris./Ola. treatment	31 (72%)	32 (65%)	0.51
Since initiation of Ris./Ola. Treatment	13 (30%)	10 (20%)	0.34
After initiation of Ris./Ola. Treatment	5 (12%)	7 (14%)	0.77

(*): Probability associated with no difference between treatments (Fisher's exact test).

Table 5. Characteristics of the hospitalization (responders)

Parameter	Risperidone (N=35)	Olanzapine (N=32)	*p(*)*
Total duration (days)	18.3 ± 14.5	15.2 ± 8.2	0.66
Duration of studied treatment (days)	14.0 ± 10.6	11.9 ± 6.9	0.58
Time (days) between admission and start of treatment	4.4 ± 11.0 (0; 1.0; 64)	3.3 ± 4.0 (0; 1.5; 15)	0.60
Length of stay in each ward (days)			
– Psychiatric	18.3 ± 14.5	14.3 ± 8.4	0.40
Discharge			
Number of patients discharged before or at day 120	35 (100%)	32 (100%)	–
N patients discharged vs. location:			>0.99
– Another hospital	2 (6%)	1 (3%)	
– To own home	32 (91%)	31 (97%)	
– Other	1 (3%)	0	
Time to discharge:			
Time estimate (95% CI) for discharge of			0.41 (1)
25% of patients	9.0 (8; 12)	9.5 (8; 12)	0.66 (2)
50% of patients	13.0 (11; 20)	13.5 (10; 16)	
75% of patients	21.0 (15; 28)	19.5 (15; 22)	

(*): Probability associated with the hypothesis of no difference between treatments (t-test for weight, Mann-Whitney rank test for duration and lengths of stay, Fisher's exact test for number of patient discharged, and log-rank test (1) and Wilcoxon test (2) for survival analysis of time to discharge).

was similar with both treatment groups (93 vs. 90% for risperidone and olanzapine, respectively, $p = 0.72$). The proportion of patients who started at least one other neuroleptic or one other concomitant medication at different times was also similar in both groups. When considered separately, the two treatment groups were not significantly different with regards to the proportion of patients who started on other neuroleptics or other relevant concomitant medications.

Table 5 shows the characteristics of hospitalization of the responders. Among responders, the total duration of hospitalization was longer in the risperidone group than in the olanzapine group (mean: 18.3 vs. 15.2 days,

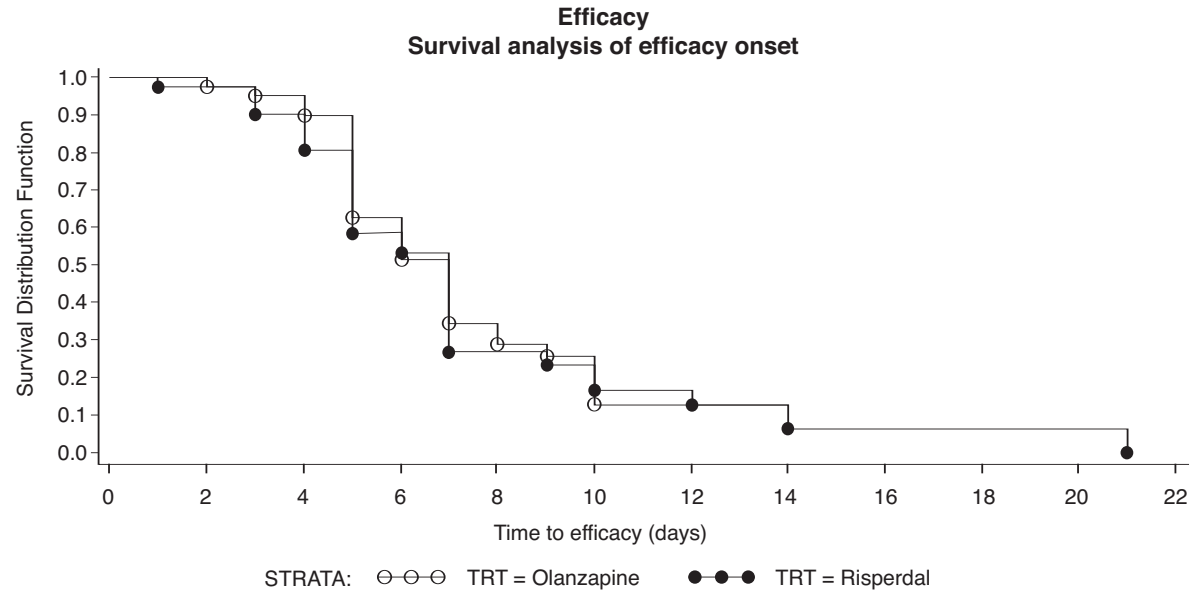

Figure 1. Time distribution function of the time (days) to onset of efficacy

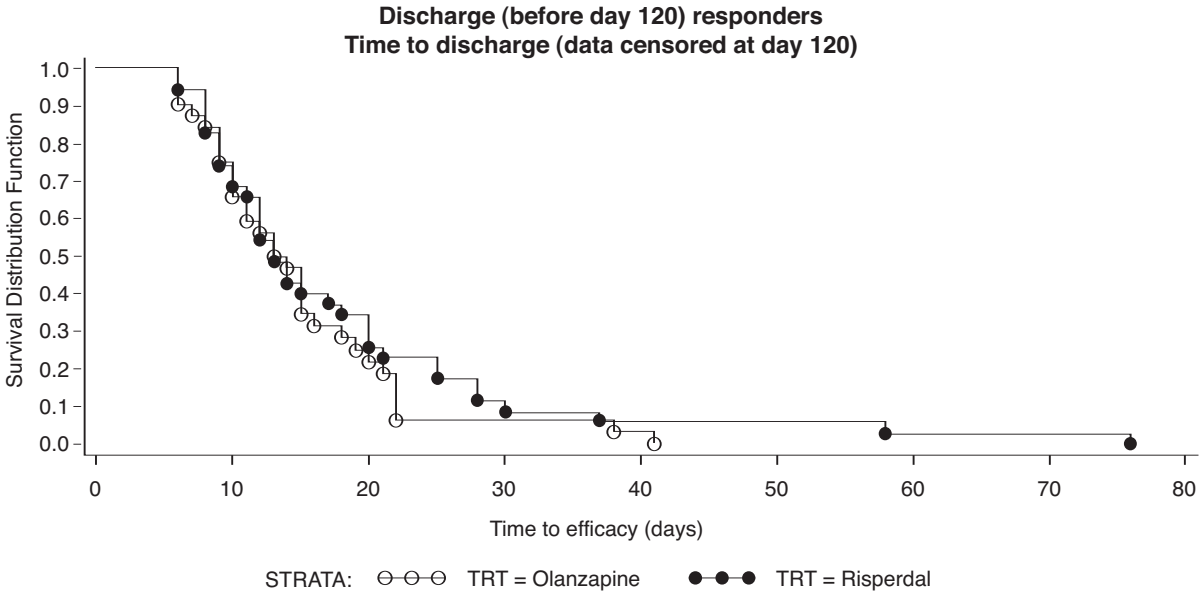

Figure 2. Time distribution function of the time to discharge of responders

respectively). The difference was not statistically significant (p = 0.66). This pattern was also true in the actual treatment; duration of risperidone was longer than olanzapine (mean: 14.0 vs. 11.9 days, respectively). The difference was also not statistically significant (p = 0.58). In the time between admission and start of treatment, no statistical difference between groups was found (mean: 4.4 vs. 3.3 day for risperidone and olanzapine, respectively, p = 0.60).

As observed in the ITT population, all responders in both groups were discharged before 120 days. Most patients were discharged to their own home (91% and 97% for risperidone and olanzapine, respectively). The

estimate median time to discharge of patients was similar in both treatment groups (13.0 vs. 13.5 days for risperidone and olanzapine, respectively). Moreover, the difference between study groups in the curve of the time to discharge distribution function was not statistically significant ($p \geq 0.40$) (Figure 2).

Discussion

An episode of psychosis is usually managed through hospitalization and use of anti-psychotic therapies. There is no evidence that really shows one atypical anti-psychotic having better efficacy than the other (7). Therefore, a pharmacoeconomic assessment would primarily be a comparison of the direct costs associated with their administration. The most important driver of costs is probably the drug acquisition costs, which are determined by the actually used dosage schedules of the anti-psychotics and by the need for concomitant medication. Another driver of costs may be the length of hospitalization.

Within this cohort of patients, treatment with risperidone was associated with significantly lower cost compared with olanzapine with no compensation in efficacy and safety. The data suggests that treatment with risperidone may be more cost-effective than treatment with olanzapine. However, there is a clear need to confirm these findings with further retrospective studies in other patient groups and with prospective, randomized, naturalistic studies that would accurately reproduce the clinical conditions in which these agents are used.

Our study has several limitations that must be taken into consideration. By definition, our retrospective study's most obvious limitation is that it is unmasked and unrandomized. The retrospective study design has the potential to compare incomparable groups through some sort of treatment allocation bias. If such a bias was in operation, we would expect to see noticeable differences in patient profiles between treatment groups that would predict the superiority of one treatment over the other. In this study, there is a significant difference in the age of admission that definitely needs consideration. The earlier the age of contact, the more likely it is to have a poor prognosis. There also has been significant difference in the diagnosis. This could affect the conclusions.

Conclusion

The duration of the study is too short for any significant conclusion on cost-effectiveness. A longer duration would have been more appropriate to see actual effects and side effects that might occur. Despite these limitations, the retrospective study does have the advantage of collecting real-world data beyond the artificial framework that a randomized clinical trial may impose.

Acknowledgement

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MEASURING MATERNAL MORTALITY IN MALAYSIA

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ABSTRACT: There has been a significant decline in maternal mortality in Malaysia since independence. The issue of measuring maternal mortality accurately is a problem in all countries. Another major problem is whether we can reduce the mortality further. The definition of maternal mortality includes two major components, which are causation of death and the time of death. To improve data collection on maternal deaths, we need to collect all data on maternal deaths, which are omitted or misclassified. Deaths from accidental causes that are not normally used in the calculations of maternal mortality need to be carefully reexamined to be excluded. The time of death means that in maternal mortality calculations, it includes up to six weeks after delivery, but recent World Health Organization (WHO) publication (ICD-10) suggests that the collection of maternal deaths even after six weeks should be reviewed because there are many maternal deaths which occur after six weeks. Measuring maternal mortality rate should be encouraged rather than maternal mortality ratio. Another measurement of maternal mortality is the lifetime risk of the women. The lifetime risk is the measure of maternal mortality that takes into account the probability of becoming pregnant and the probability of dying as a result of pregnancy. Many countries have started reporting the lifetime risk, which is considered to be better indicator to measure maternal health. *(JUMMEC 2006; 9(1): 30-34)*

KEYWORDS: Maternal mortality rate, maternal mortality ratio, lifetime risk

Introduction

Globally, approximately 210 million women become pregnant and some 130 million give birth. Although most of these pregnancies are uneventful, an estimated 15% develop complications, and about one-third of these have life threatening consequences. Complications related to pregnancy and childbirth result in more than half a million deaths and 99% of them occur in developing countries (1). Every minute somewhere in the world, a woman dies from complications in pregnancy and childbirth. The majority of these deaths are avoidable (2). In some developing countries, the lifetime risk of maternal deaths may be as high as one in seven, when compared to one in 5,000 in many developed countries. This disparity of more than a hundredfold in maternal deaths reflects the tragic status between developed and developing countries (3). Maternal mortality has been a neglected problem globally for so long due to inadequate information. Countries with the highest levels of mortality, seldom have reporting of vital events such as births and deaths. In the mid-1980s, a number of community surveys, many of which were supported by WHO brought to light the size of the problem but the significance of maternal deaths remains largely ignored and unattended.

In Malaysia, the maternal mortality ratio declined from 530 per 100,000 live births in 1957 to 148 per 100,000 in 1970 and 30 per 100,000 live births in 2000 (4). There has been a significant decline in the reduction of maternal mortality in this country in the last 50 years (Figure 1). The decline in maternal mortality has been due to the introduction of various programmes in the area of reproductive health since the 1950s. Have we reached the minimum limit of maternal mortality or can we reduce it further? The answer lies to a large extent in the measurement of maternal mortality. Are we measuring maternal mortality accurately or do we need to relook at the way we measure maternal mortality? There is a probability that if we are able to capture all maternal deaths, Maternal Mortality Ratio (MMR) may be much higher than what it is now. This study proposes to identify the problems of measuring maternal mortality and suggest ways as to how we can further measure MMR more accurately.

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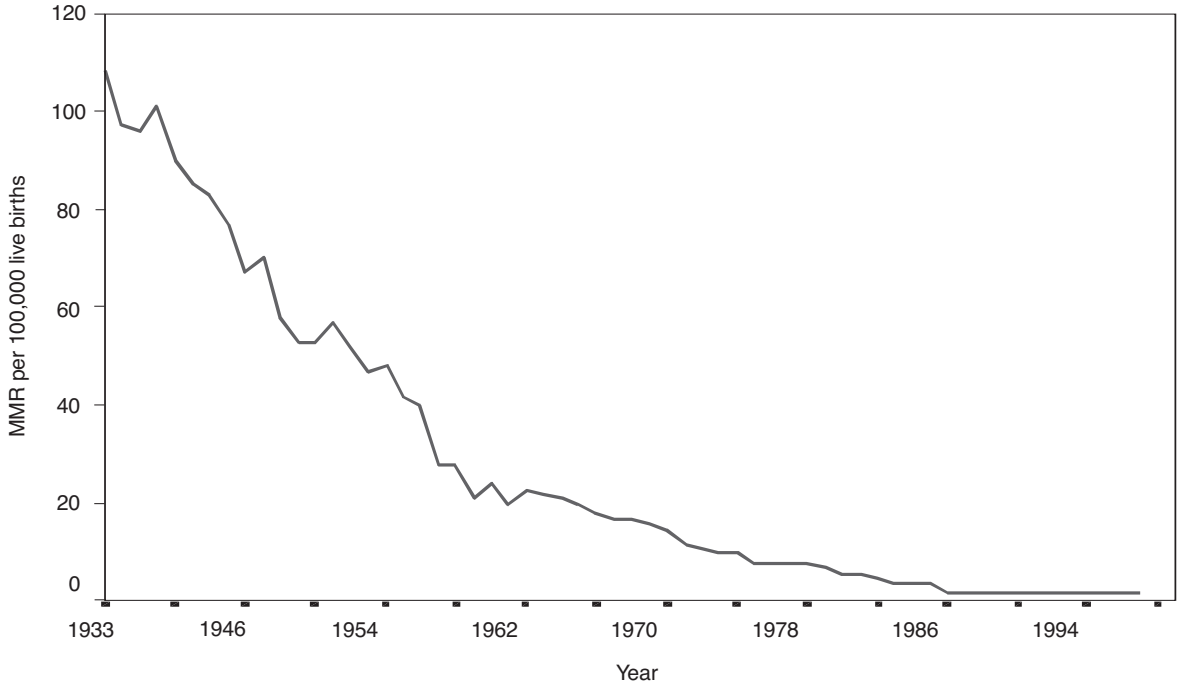

Source: Vital Statistics Time Series (1911-1985) Department of Statistics Kuala Lumpur and Ministry of Health, Family Health Unit Annual Report 1998

Figure 1. Maternal mortality ratio by year

Background

Maternal death is defined as the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental cause (5). The direct obstetric deaths resulting from complications arising during pregnancy, labour or during the post-partum period deaths may result from interventions, omissions, incorrect treatment or from a chain of events resulting from any of the above. The indirect obstetric deaths result from previous existing disease or diseases, which develop during pregnancy, e.g., heart disease and diabetes. The accidental or coincidental deaths are deaths due to accidents such as road accidents or drowning of a pregnant women (1).

About 80% of all maternal deaths in the world are due to direct cause which are complications arising during pregnancy, delivery and during the first six weeks after birth. The five main causes of maternal deaths in the world are haemorrhage (25%), sepsis (15%), eclampsia (12%), obstructed labour (8%) unsafe abortion (13%) and indirect causes account for 20% of all deaths (2). Unsafe abortion accounts for more than a third of maternal deaths in some parts of the world. About 20% of the remaining maternal deaths are due to indirect causes. Anaemia is one of the most significant causes and the other indirect causes are malaria, hepatitis, heart disease and HIV/AIDS. The low status of women limits women's access to economic resources and education. Poor nutrition before and during pregnancy contributes to poor health, obstetric problems and poor pregnancy outcomes for both women and their newborns.

In Malaysia, reports from the Confidential Enquiry into Maternal Deaths (CEMD) during a four-year period of 1991-1994, found that the most common cause of maternal mortality was post-partum haemorrhage (PPH) (24.9%) followed by hypertensive disease of pregnancy (HDP) (16.3%), obstetric embolism (12.4%), and associated medical conditions (10%), birth trauma was 6.4% and puerperal sepsis was 6.1%. The indirect maternal deaths were responsible for 10.5% of the total maternal deaths for the same period (6).

Reliability of maternal mortality rates

Theoretically, maternal mortality rate is the number of maternal deaths (numerator) to the total number of pregnancies (denominator) per 100,000 pregnancies.

However, in practice, it is very difficult to get the exact number of pregnancies. Therefore, what is measured is actually the maternal mortality ratio and not the maternal mortality rate in the comparison of maternal deaths to total births. Maternal mortality rate is difficult to obtain because the denominator of exact number of pregnancies including live births, foetal deaths, stillbirths, induced and spontaneous abortions, ectopic and molar pregnancies are difficult to obtain. Therefore, total births as a proxy denominator for the total number of pregnancies are used.

Maternal Mortality Ratio is also an underestimate due to poor vital registration of maternal deaths. Many deaths go unregistered and uncertified. Although some countries have a good registration system, the poor classification of death makes the validity of the maternal mortality rate questionable.

The MMR measures a woman's chances of dying from a given pregnancy. For example, if a pregnant woman who has a miscarriage during the first 28 weeks, does not register the deaths of the foetus. If she has not registered for pre-natal care, she may be missed in the denominator, thus, affecting the MMR rate. Also pregnancies that result in death of the foetus after 28 weeks are also often not registered. In some underdeveloped countries, the registration of births and death may not be easily available due to poor accessibility and cost of travel to make a report. The mothers also do not regard this issue as important. Pregnancy is also seen as a private matter in some societies and as such terminations and abortions may not be reported. It is very difficult to know the exact number of pregnancies and therefore live births, which is easily available is used as the denominator. Live births are therefore considered a reasonable proxy indicator of pregnancies in an area.

Problems in maternal mortality measurement

There are two problems in the definition; one, that is related to the time of death and the second, to the cause of death. With regard to the time of death, historically MMR was defined as deaths occurring within six weeks of pregnancy. This six weeks timing was sanctioned by a variety of practices both religious and cultural. There is no scientific basis for this six weeks period (7). However in modern day medicine, life can be sustained longer with better procedures and techniques, which can prolong dying and delay death. Even before the era of modern medicine, it is likely that death took place beyond the six weeks interval but the proportion was very small. Medical procedures may increase that proportion but it is likely to remain fairly small although by no means negligible. The Centre for Disease Control and Prevention reported that 29% of maternal deaths occurred after 42 days of pregnancy termination and about 6% occurred 90 days post-partum (7). The ICD-10 therefore, introduced a new category called the "late maternal death, which is defined as death of a woman from direct or indirect obstetric causes more than 42 days but less than one year after termination of pregnancy."

The second problem with the definition of maternal death, lies in the classification of the cause of death. Omission of maternal deaths can be due to the fact that pregnancy and abortion are concealed. There can be also a misclassification of maternal deaths between maternal and non-maternal deaths and also obstetric and incidental deaths. Sometimes, even the cause of death is ill-defined and difficult to categorize. According to ICD-9 and ICD-10, maternal deaths are divided into two groups, i.e., direct obstetric death and indirect obstetric deaths. The drawback of this definition is that the maternal death can escape being classified as being the precise cause of death. Deaths from "accidental or incidental causes" have historically being excluded from maternal mortality. However, in practice, the distinction between incidental and indirect cause of death is difficult to make. It is likely that many homicides and suicides of pregnant women may be classified as accidental or fortuitous but in actual fact, it could be due to the embarrassment of premarital pregnancy or that the pregnancy may have produced a child of the wrong sex. Thus, the suicide or homicide examination has to be done in detail to ascertain that it is excluded in the measurement of MMR (7). Deaths missed due to causation in some countries ranged from 22% in England and Wales to about 70% in Egypt, Jamaica and Puerto Rico (8).

Changes related to MMR in ICD-10 (7)

There is very little change in the definition in the ICD-9 and ICD-10 codes for classifying causes of maternal deaths. The Tenth Revision of International Classification of Diseases (ICD-10) defines MMR similar to the ninth revision. The Ninth International Classification of Diseases (ICD-9) classified the complications of pregnancy, childbirth and the puerperium into five broad classes:

1. Pregnancy with abortive outcome (630-639),
2. Complications related to pregnancy (640-648),
3. Normal delivery and other indications for care in pregnancy, labour and delivery (650-659),
4. Complications occurring mainly in the course of labour and delivery (660-669), and
5. Complications of puerperium (670-676).

However, the Tenth International Classification of Disease (ICD-10) has divided the pregnancy-related problems into eight blocks, covering slightly different group of diseases. They are:

1. Pregnancy with abortive outcome (000-008),
2. Oedema, proteinuria and hypertensive disorders of pregnancy, childbirth and puerperium (010-016),
3. Other maternal disorders predominantly related to pregnancy (020-029),
4. Maternal care related to the foetus and amniotic cavity and possible delivery problems (030-048),
5 Complications of labour and delivery (060-075),
6. Delivery (080-084),
7. Complications predominantly related to the puerperium (085-092), and
8. Other obstetrical complications not elsewhere classified.

There is an increase of three more categories according to ICD-10 as compared to ICD-9 and this will make comparison of data very difficult within the country and also between countries. The ICD reporting system also assumes a single cause of death although there is a chain of events to the final cause of death. Only a single cause of death is reported and the cause is very subjective. There is a possibility that the cause of death may be misclassified. This misclassification may also reduce the maternal mortality further.

Discussion

Although there has been a significant decline in maternal mortality in Malaysia, the actual rates may be higher. All maternal deaths in all wards in the hospitals need to be reviewed to exclude the possibility of missing maternal deaths. This is to make sure that we do not miss the maternal deaths that have died in medical, surgical or other wards due to direct or indirect causes and have been misclassified. This will provide more accurate MMR in the country. A concerted effort is mandatory to include all maternal deaths that are missed by omission, misclassification of deaths and also deaths that are ill-defined is necessary to avoid any missed deaths. All the incidental or accidental death currently classified, must be confirmed to exclude it as a maternal death. Although the Ministry of Health Confidential Enquiry into Maternal Death (CEMD) does this, it must be clear the accidental maternal deaths are really accidental deaths and only then they can be excluded from the MMR calculations. Careful reviews may mean that some of the incidental deaths may be included in the MMR calculation. Countries that do not have the registration of births and deaths sometimes use special surveys and other methods to measure maternal mortality.

Malaysia has a good database and it needs to address the issue of missing deaths and take into consideration the new ICD-10 proposal of including those maternal deaths beyond 42 days. In countries where the maternal mortality is high, the bias introduced by the inclusion of accidental or incidental causes is usually low. In rural Bangladesh, where the overall mortality rate is 570 per 100,000 live births, it was found that 90% of the deaths were due to direct and indirect maternal causes. Therefore, the issue of incidental maternal deaths is less (7). However, in Malaysia where the maternal mortality rate is 20 per 100,000 live births and direct and indirect account for 78.5% and incidental deaths account for 21.4%, there is a need to review all accidental deaths more seriously.

To overcome this problem of causation of deaths, the ICD-10 has suggested a new category "the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of death". ICD-10 has also introduced the late maternal death category which is defined as the death of a woman from direct and indirect obstetric cause more than 42 days but less than one year after termination of pregnancy. This is to recognize the cases, which may die due to pregnancy causes after 42 days of birth. We may have missed some of the maternal deaths due to this cause. It was found in the state of Georgia in US, that 29% of maternal deaths occurred after 42 days of pregnancy and 6% occurred after 90 days over the period of 1974-75. We have to look at maternal deaths after 42 days to see whether they are related to maternal deaths.

Conclusion

With the confusion in the use of the terms ratio and rate, a proposed ideal measure is the lifetime risk. The concept of lifetime risk is another way in which some countries are measuring maternal mortality and it is important that we adopt this concept. This takes into account both the probability of becoming pregnant and the probability of dying as result of pregnancy cumulated across a woman's reproductive years – the lifetime risk. The product of the total fertility rate and the maternal mortality ratio can also approximate it. This concept is becoming increasingly popular in developed countries and we should seriously consider applying this concept in our country. With the imple-

mentation of some of these ideas, we may be able to get a more accurate maternal mortality data and therefore address the problem of inaccurate maternal mortality measurement in the country.

Acknowledgement

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THE PREVALENCE OF VISUAL DEFECT AMONG COMMERCIAL VEHICLE DRIVERS IN SELANGOR, MALAYSIA

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ABSTRACT: A cross-sectional survey of commercial vehicle drivers who were renewing their own licences was conducted at the Selangor Road Transport Department office in Padang Jawa between 1 February 2002 and 28 February 2002, using questionnaire and medical examination. The objective was to determine the prevalence of myopia, colour vision deficiency and visual field defect among the commercial vehicle drivers. The respondents that reported visual defect at the time of interview was compared with those detected by the author through medical examination. Out of the 223 respondents, 21 (9.4%) reported to have myopia by the questionnaire survey. Through the visual examination there were 63 (28.3%) with myopia (visual acuity worse than 6/12), six (2.6%) had a visual field defect and 14 (6.3%) had red-green colour deficiency. The visual defect detected during the study among the commercial vehicle drivers, which were missed at the time of the routine medical examination were significant. The process of the statutory medical examination should be reviewed. *(JUMMEC 2006; 9(1): 35-38)*

KEYWORDS: Medical examination, myopia and driving, commercial vehicle drivers, visual acuity

Introduction

Road accidents have been emerging as one of the leading cause of fatalities in the world today. In 1998, it was the tenth Leading Cause of Death; causing more than one million fatalities (1). The World Health Organization has forecast that, by the year 2020, road accidents will be the second most common cause of premature death in the world (1).

In Malaysia, road traffic injuries were responsible for 45.8% of hospitalization and 68.9% of injury deaths in government hospitals. Every day about 15 people die on the road (2).

Commercial vehicle drivers spend a lot of time on the roads. Some of them have to operate large and long vehicles, which are more difficult to manoeuvre during stopping, acceleration, and lane changing, and difficult in judgement of clearance for both height and length. These vehicles will have a greater potential for damage and injury in cases of road accidents.

The reasons for road traffic accidents can broadly be divided into three; those related to the road user, vehicle design and road environment (3,4). The factors that are related to the road user include those due to the drivers and pedestrians. The drivers' factors are annual mileage, fatigue and inattention, age, intoxication and speeding (5).

Many medical conditions, including vision impairment had been associated with road traffic accidents (6,7,8, 9,10,11,12,). Vision plays a very important role in safe driving, it is often said that approximately 90% to 95% (13,14) of the sensory input to the brain required for driving comes from vision. With this much at stake that is why visual acuity had been a key issue in the issuing of driving licences in many countries.

Vision requirement for driving

Different countries have different visual standards for private and commercial vehicle drivers (15,16,17,

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18,19). In this study the author only looked at factors that had been established by the Road Transport Department (RTD) of Malaysia, which included visual acuity for distant visual defect (myopia), colour vision and visual field (20).

All drivers in Malaysia are required to possess a valid driving licence in its class. There is no prior medical examination for driving private vehicles; the drivers are only required to read the licence plates test and colour plates during the learners' licence test. Commercial vehicles drivers would have to undergo annual medical screening before they are allowed to renew their vocational licences. Medical practitioners registered with the Malaysian Medical Council (MMC) perform this medical screening after which they will have to endorse the JPJ L8A form from RTD stating that the driver is medically fit to drive commercial vehicles.

The visual acuity requirements stated in the guideline from RTD, are minimum of 6/60 in each eye without glasses and 6/12 or better in each eye with corrective glasses. Commercial vehicle drivers who need corrective glasses for driving need to declare this in their driving licences. The other visual requirements are normal colour vision and a normal field of vision.

Materials and Methods

A cross-sectional descriptive study on the prevalence of myopia among the commercial vehicle drivers was conducted at the Selangor State RTD Office in Padang Jawa. Commercial vehicle drivers who were renewing their own vocational licences between 1 February 2002 and 28 February 2002 were selected as the study population. Those who were applying for new licences were excluded. The interview and the vision examination were conducted by the author at the RTD office. The vision examinations included visual acuity examination using the Snellen Charts (alphabet or the illiterate E chart), colour vision using Ishihara Chart and visual field examination using the Humphrey Perimeter. Data management and analysis were done using the SPSS (Version 10.0).

Results

Characteristics of respondents

There were 223 drivers who responded to the questionnaire and the medical examinations. None of the drivers approached by the author refused to co-operate. All of the respondents were male. Their ethnic group distribution is shown in Table 1. The mean age of the respondent was 36.3 years (SD 7.8) and range from 22 years to 58 years.

Table 1. Ethnic group distribution of respondents

Ethnic	Total	Percentage
Malay	138	61.9
Chinese	23	10.3
Indian	51	22.9
Others*	11	4.9
Total	**223**	**100**

** The others stated in the table included 8 Indonesians, one Kadazan, one Kampuchean, and one Pakistani. All the respondents were Malaysian nationals.*

Statutory medical screening

Out of the 223 respondents, seven (3.1%) reported that their medical screening was not carried out, and their doctors had only endorsed the RTD medical forms.

Previous medical conditions

Out of the 223 respondents, six (2.7%) were known to suffer from diabetes mellitus; five were on oral medications and one on sub-cutaneous insulin injection. Seven (3.1%) had hypertension and were on regular medication. None of the respondent reported to have either epilepsy or cardiovascular diseases.

Seven (3.1%) had defective colour vision, 21 (9.4%) had myopia and 14 (6.3%) had presbiopia. Five of the respondents had pterygium and one had squint. None of the respondents has cataract or glaucoma. Out of the 21 respondents who were known to have myopia, only 14 were using their corrective glasses while driving.

Medical examination

During the medical examination the author detected 52 with visual acuity of worse than 6/12; for those that used corrective glasses, visual acuity tests were performed with their corrective glasses. Seventeen respondents had visual acuity of worse than 6/12 in the right eye alone and ten had visual acuity of worse than 6/12 in the left eye alone. Twenty-five had visual acuity worse than 6/12 in both eyes. Two respondents had visual acuity of 6/60 in the right eye and two respondents had visual acuity of 6/60 in the left eye. One of the respondents had visual acuity of 6/60 in both eyes.

Out of the fourteen that used corrective glasses, three had visual acuity of worse than 6/12 in either one eye even with their corrective glasses. When comparing ethnicity and visual defect, the Chinese has the highest percentage of visual defect (47.8%) compare to other races (Table 2), the result are comparable to other studies (21, 22, 23). Six respondents (2.6%) had a visual field defect and 14 (6.3%) had red-green colour deficiency.

Table 2. Race and visual defect

Visual Defect*	Race (percentage) Malay	Chinese	Indian	Others	Total
No	106 (76.8)	12 (52.2)	36 (70.6)	6 (54.5)	158 (71.7)
Yes	32 (23.2)	11 (47.8)	15 (29.4)	5 (43.5)	63 (28.3)
Total	**138 (100)**	**23 (100)**	**51 (100)**	**11 (100)**	**223 (100)**

** Visual defect includes those who wear glasses as stated in questionnaire and has visual acuity of worse than 6/12.*

Adequacy of statutory medical examination

The author used visual acuity as an indicator for adequacy for statutory medical examination. Comparing the prevalence of reported myopia and the results of visual acuity examination, taking visual defect to be worse than 6/12. When people with myopia who used corrective glasses were excluded from the results, the author found that there is a significant difference between the result of the visual acuity examination and the reported myopia (Table 3). The medical examination revealed 49 of the respondents with visual acuity worst than 6/12 and five respondents who had visual acuity of 6/60 were missed during the statutory medical screening. This indicated that the statutory medical examination had failed to detect a significant number of drivers who had myopia.

Table 3. Myopia (from statutory medical screening) and visual defect* detected by examination

Myopia	Visual Acuity Defect No	Yes	Total
No	157	45	202
Yes	3	4	7#
Total	**160**	**49**	**209**

Measurement of Agreement:
Kappa 0.089, Std Error = 0.057, Sig = 0.032

** Visual acuity defect is taken as visual acuity worst than 6/12 when reading the Snellen chart at 20 feet (six meter).*

 # The 14 individuals with myopia and wear corrective glasses have been excluded from the findings.

Discussion

A total of 223 drivers were interviewed; their ages were between 22 and 58, with the majority less than 40 year old.

Myopia

In this study, the author found 63 (28.3%) drivers with myopia. This includes the 14 who wore corrective glasses. Of those who wore corrective glasses, 11 had visual acuity of 6/12 or better with the corrective glasses and three had visual acuity worse than 6/12. The result is comparable to the study done on young males in Singapore, which is 30.4% (23), but in another study on 110,236 Singaporean males, the percentage is higher at 44.2% (24).

Statutory medical examination

The results of this study showed that the statutory medical examination had failed to detect a significant number of drivers with myopia and other visual defects. The statutory medical examination also missed a driver with insulin-dependent diabetes mellitus, which should have been disqualified under the RTD guidelines and JPJ L8A (20) forms.

The above result showed that although statutory medical examinations were required for the commercial vehicle drivers, the medical examinations conducted were not up to the required standard. The examination failed to reveal diseases that were not allowed by law to drive commercial vehicles. This can be serious, as other studies have shown an association between such medical conditions and road accidents. One possible reason for the failure of the medical practitioner to conduct a more thorough medical examination may be due to the fact that fees for each medical examination was only between RM5 and RM15 (US$1 = RM3.80), although a thorough medical examination would takes at least 20 minutes to conduct. The Malaysian Medical Council Fee Schedule 1997 recommended the fees for medical examination for commercial vehicle drivers to be RM50 (25). Another reason could be that the medical practitioner may not be aware of the minimum medical requirement for commercial vehicles drivers as the visual field test requirement was not stated clearly in the RTD guideline.

Conclusion

This study confirms that the prevalence of visual defect among the commercial vehicle drivers are similar to that of earlier studies on normal population within this region. It appears that many of the drivers are not aware of defects in their vision despite having undergone a thorough medical examination. Furthermore, those who were aware of their visual defect did not correct the defect, and were still driving with vision that do not meet the standard RTD requirements.

The authority should look into this matter and revise the format and form of the statutory medical examination as this can be detrimental to the safety of road users.

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DIAGNOSING ANGINA USING A SIMPLE NEURAL NETWORK ARCHITECTURE

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ABSTRACT: The aim of the study was to research the use of a simple neural network in diagnosing angina in patients complaining of chest pain. A total of 887 records were extracted from the electronic medical record system (EMR) in Selayang Hospital, Malaysia. Simple neural networks (simple perceptrons) were built and trained using a subset of 470 records with and without pre-processing using principal components analysis (PCA). These were subsequently tested on another subset of 417 records. Average sensitivity of 80.75% (95% CI 79.54%, 81.96%), specificity of 41.64% (95% CI 40.13%, 43.15%), PPV of 46.73% (95% CI 45.20%, 48.26%) and NPV of 77.39% (95% CI 76.11%, 78.67%) were achieved with the simple perceptron. When PCA pre-processing was used, the perceptrons had a sensitivity of 1.43% (95% CI 1.06%, 1.80%), specificity of 98.32% (95% CI 97.92%, 98.72%), PPV of 32.95% (95% CI 31.51%, 34.39%) and NPV of 61.33% (95% CI 59.84%, 62.82%). These results show that it is possible for a simple neural network to have respectable sensitivity and specificity levels for angina. ***(JUMMEC 2006; 9(1): 39-43)***

KEYWORDS: angina, diagnosis, prediction, decision-support, neural networks, perceptrons

Introduction

Acute chest pain in the adult is a frequently encountered symptom in all healthcare settings (1). The diagnosis of angina is occasionally not as straightforward as it would appear and in many cases, classical electrocardiogram findings (ECG) of angina may not be evident early on. However, there is broad consensus that lifestyle factors, including physical activity and diet, are fundamental determinants of heart disease risk (2).

In recent years, there has been renewed interest in neural networks in cardiovascular diseases, particularly, ischaemic heart disease. The majority of this research has concentrated on the use of neural networks in diagnosing acute myocardial infraction (AMI) and almost all have used biochemical markers and ECG findings in concert with the history and physical examination. Ellenius and Groth (3,4) investigated neural networks in the assessment of biochemical markers in AMI. Work conducted (5) and in the Heart Disease Program (6) have contributed much to the use of artificial intelligence (AI) techniques in chest pain diagnosis.

Studies have shown very good results with neural networks in the diagnosis of AMI using just patient-reportable factors and comparing favourably with statistical methods (7). High sensitivity and specificity levels (exceeding 80%) for cardiac ischaemia (a mixture of AMI and angina) were also achieved with feedforward neural networks on chest pain patients with ECG and chemical cardiac markers (8,9) and exceeding 90% (10) used neural networks to identify patients with significant coronary artery disease and reported positive predictive accuracy rates of 80% and negative predictive accuracy of 92% (11). However, little research has been made using neural networks in diagnosing angina although angina is probably more prevalent than AMI in most developed countries. Furthermore, attempts to build neural networks without the use of any ECG and biochemical markers have been made (12).

Due to the difficulty in diagnosing chest pain and the importance of not missing an important disease like angina where biochemical markers and ECG findings

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may not be as helpful as AMI, this has become an area where some form of decision-support with artificial intelligence (AI) would be most helpful. It would thus be possible to construct a tool or software to aid a paramedic or even the public in diagnosing angina even without the benefit of an ECG with a high degree of probability (possibly exceeding 80%).

The objective of this study was to assess the sensitivity, specificity, positive and negative predictive values of simple (single-layer) perceptrons in chest pain diagnosis with respect to the diagnosis of angina. It is also aimed at how far one could use perceptrons in a screening tool that could be used by paramedics or even the public in diagnosing angina.

Materials and Methods

Source of data

The data set was obtained from Selayang Hospital, a tertiary level hospital in Malaysia. Permission to use this data for this study was obtained from the Ministry of Health, Malaysia. All records of adult patients (18 years or older) seen in the Emergency Department for non-traumatic chest pain from 20 August 1999 (when the hospital opened) to 9 August 2002 and clerked using the chest pain clerking form were selected for this study. As this form was used for chest pain suspected to be of cardiac origin, the number of patients clerked using this form was low and the proportion of angina patients clerked using this form was high. Both stable and unstable angina were included as angina as the diagnosis was not clearly stated in many cases. The diagnosis on discharge was used as the definitive diagnosis.

Data cleaning and pre-processing

Data cleaning and pre-processing were performed before the neural networks were constructed. This involved accuracy checking, treatment of missing values, recategorization and recoding of fields and feature construction. The data was split into two sets; a training set and a test set by random sampling. The training set comprised 470 records while the test set contained 417 records. The training set had 187 cases of angina and the test set, 161 cases of angina. Table 1 shows the input variables in the data set.

Experimental methods

The single neuron, single-layer perceptron was used for all experiments. The diagnosis on discharge was used as the definitive diagnosis. This is the diagnosis as confirmed by specialist physicians after taking into consideration ECG readings and other laboratory investigations.

All perceptrons were trained over a maximum of 1,000 epochs for each combination of input and target. The perceptrons were then tested on the test set. This process was repeated until ten perceptrons had been trained and tested. Weights were initialized randomly and reinitialized every time the network was trained, so no two networks had the same weights. Matlab 6.5 was used to build, train and test the per-

Table 1. Input variables

Group	Fields
Demographic	Age, citizen, race, sex, marital status
Nature of chest pain	Location, onset, pattern, quality
Radiation of pain	Jaw, left arm, laterally, neck, locally, other parts
Relieving factors	Leaning forward, sitting up, GTN, rest, other means
Aggravating factors	Posture, meals, coughing, inspiration, exertion
Associated heart/lung symptoms	Cough, dyspnoea, oedema, orthopnoea, palpitations
Other associated symptoms	Collapse, headache, dizziness, fever, numbness, nausea, sweating, vomiting, fainting
Cardiac risk factors	Age >40, diabetes mellitus, family history, hypertension, physical inactivity, obesity, smoking, known case defaulted treatment, known case on treatment, high cholesterol levels
General examination	Pulses, pulse rate, respiratory rate, systolic BP, diastolic BP
Heart/lung examination factors	Air entry, breath sounds, chest expansion, chest wall, crepitations, heart sounds, JVP, percussion, pleural rub, praecordium, rhonchi
Other examination factors	Abdomen, central nervous system (CNS), eye, face

ceptrons. Only patient-reportable factors and examination factors were used in this study as the aim was to investigate, how well the perceptron would be able to diagnose the disease without any investigation results to rely on (Table 1).

After using the original data to train the perceptrons, principal components analysis (PCA) was used to reduce the dimensions of the input vectors. The data was thus pre-processed and the perceptrons were retrained and retested. Only input data that contributed to more than 0.5% of the total variation in the data set were retained.

The results were pooled for each group by the type of pre-processing (10 perceptrons for each group) and outcome measures with 95% confidence intervals were calculated.

Statistical analysis

Sensitivity and specificity (13), as well as positive and negative predictive values (14) with 95% confidence intervals were calculated using standard formulas. The use of a large sample size by pooling the results, is not new (9) and was made in order to obtain a more representative picture of the perceptron performance. This also avoids the problem of confidence intervals exceeding 100% due to small sample sizes (15). Continuity correction was used for all calculations of sensitivity, specificity, positive and negative predictive values.

Results

The performance of the angina perceptron is displayed in Table 2. The training set had 187 cases of angina while the test set had 161 cases of angina. There was no significant difference in training time using the original data and data that had been pre-processed using PCA over 1000 epochs. There was a significant difference in the mean MSE of the two groups with the original data having slightly higher average MSE (0.421; 95% CI 0.402, 0.439) compared to the PCA group (0.368; 95% CI 0.354, 0.382) but neither of the MSEs reduced to zero.

Perceptrons trained using the original data managed a respectable mean sensitivity level of 80.75% (95% CI 79.54%, 81.96%). This contrast significantly with the perceptrons trained using PCA-processed data, which only managed a dismally low sensitivity of 1.43% (95% CI 1.06%, 1.80%). The difference between these two groups was not only statistically significant but also clinically significant. In contrast, the specificity levels were reversed between the two groups, with the perceptrons trained using PCA-processed data managing a very high specificity level of 98.32% (95% CI 97.92%, 98.72%) compared to the low specificity of the perceptrons trained using the original data (41.64%; 95% CI 40.13%, 43.15%). Despite the difference in the sensitivity and specificity results, the PPV and NPV levels were significantly better for perceptrons trained using the original data. The PPV for the perceptrons trained on the original data was 46.73% (95% CI 45.20%, 48.26%) while the PPV for the PCA group was 32.95% (95% CI 31.51%, 34.39%). NPV for the perceptrons trained on the original data was 77.39% (95% CI 76.11%, 78.67%) while the NPV for the PCA group was 61.33% (59.84%, 62.82%). In general, the variability in test accuracy, sensitivity and specificity levels were much less for perceptrons trained on PCA-processed data compared to those trained on the original data as reflected by their much tighter confidence intervals.

Limitations

There are a few limitations to these experiments. The single-layer perceptron is limited in what it can do and while it is ideal for problems that have a binary output like a diagnosis, it has some limitations in the amount of information it can conceivably process. These perceptrons have not been tested on a real-time basis but there is no reason to think that it might not work given that it worked on the 417 records (test set) that it had never seen before. This study also did not evaluate all potential patients with ischaemia because it was confined to patients with chest pain in the Emergency Department and thus did not deal with those suffering from silent ischaemia. Finally, this study was carried out at a single institution and one may need to corroborate with patients from different locations.

Table 2. Angina perceptron performance

Performance measure	Mean without PCA (95% CI)	Mean with PCA (95% CI)
Sensitivity (%)	80.75 (79.54, 81.96)	1.43 (1.06, 1.80)
Specificity (%)	41.64 (40.13, 43.15)	98.32 (97.92, 98.72)
PPV (%)	46.73 (45.20, 48.26)	32.95 (31.51, 34.39)
NPV (%)	77.39 (76.11, 78.67)	61.33 (59.84, 62.82)

Discussion

There has been some work with multi-layer perceptrons in chest pain diagnosis and some workers have shown some good results with these (9,10,16). However, most of the work has had to use ECG and biochemical markers and none have used the simple perceptron, perhaps as it is believed that it is not capable of a complex and non-linear process of diagnosing a disease like AMI or angina. Attempts were made for a neural network using just patient-reportable factors and without the use of ECG and biochemical markers (12). It was shown that some uses could be made from the single-layer perceptrons. These perceptrons have the advantage of the hard-limit function and are relatively simple to implement. The advantage is that their relative simplicity makes them less useful where the input data is abstract and they may be unable to "learn" the associations between input and output well enough to be accurate.

The author is encouraged by the sensitivity of 80.75 (95% CI 79.54%, 81.96%) obtained without PCA processing. Unfortunately, when PCA was used to pre-process the data, it reduced the sensitivity greatly. However, it improved specificity and made the perceptrons consistently more specific compared to the perceptrons trained without PCA pre-processing. One possible explanation for this is that PCA reduces the amount of information needed for the perceptron to make a positive diagnosis and made it unable to differentiate between a positive and negative diagnosis. It would thus tend to label something as being no different from another negative diagnosis. Thus, the perceptron was able to more easily recognize what is not angina rather than what is. Herein probably lies the limitation of the perceptron in pattern recognition. A perceptron can only represent linearly separable functions and are thus not suitable for many functions which are not linearly separable. PCA removes much of the information which is necessary for the perceptron to perform its function properly. However, PCA does have one benefit. It reduces the variability of the perceptron's performance and makes it far more predictable as far as specificity is concerned.

Conclusion

It seems difficult to come up with a perceptron which is both highly sensitive and highly specific. This is not surprising, as studies have shown similar findings with regards to the balance in sensitivity and specificity (5). Where sensitivity is raised, specificity can be expected to fall as more false positive cases are identified. Research has also shown high sensitivity and specificity levels occurring at the same time (9). To expect the perceptron to achieve sensitivity and specificity greater than 80 per cent at the same time appears to be beyond the single-layer perceptron especially where there are no ECG and biochemical readings to help the perceptrons. In theory, the use of a 2-perceptron system (where one perceptron is trained with PCA and the other is trained without PCA) with the results of both evaluated by a fuzzy inference engine may be able to solve this problem, but it is probably just easier to use a more sophisticated multi-layer neural network instead.

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