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"Dark clouds become heaven's flowers when kissed by light."

Rabindranath Tagore (1861 – 1941)
Indian poet

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Editorial

HIV Prevention: The Promise of Pre-Exposure Prophylaxis in Singapore

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Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) remains a global health problem, with 2.1 million new infections globally in 2015[1] and 455 newly diagnosed cases in Singapore in the same year.[2] It is increasingly evident that novel strategies are needed to achieve significant reductions in new HIV infections. These include the use of treatment as prevention (TasP), wherein highly active antiretroviral therapy (HAART) is initiated early after the diagnosis of HIV infection to suppress viral load and reduce infectivity;[3] as well as post-exposure prophylaxis (PEP), where a 4-week course of HAART is administered after high risk exposures to reduce the likelihood of infection.[4]

HIV pre-exposure prophylaxis, or PrEP, is a new and promising addition to the HIV prevention armamentarium, which has heretofore been focused on behavioural risk reduction, and which may have plateaued in effectiveness—as evidenced by the relatively stable incidence of HIV infections despite ongoing prevention efforts.

PrEP involves the use of anti-retroviral drugs (primarily the co-formulation of tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC] known by its trade name Truvada) by HIV-negative individuals who are at high risk of contracting HIV to prevent infection. These populations include men who have sex with men (MSM) that report high risk sexual behaviour, HIV-negative partners in serodiscordant couples and women at-risk.

The evidence underpinning the use of PrEP is derived from numerous large, randomised controlled trials demonstrating its efficacy in preventing HIV infection. Of note is that none of the major trials were led or initiated by pharmaceutical companies. Amongst MSM and transgender women, the iPrEx trial of daily-administered PrEP demonstrated an overall reduction of HIV transmission risk of 44%; those with detectable plasma levels of Truvada had a 92% reduction in risk compared to those with undetectable drug levels, underlining the efficacy of PrEP when therapy was adhered to.[5] The French and Canadian iPERGAY trial of on-demand PrEP (taken before, then 24 and 48 hours after each sexual act) showed that MSM randomised to receive Truvada had a 85% risk reduction of HIV infection compared to the comparator group; again, this was dependent on adherence to the recommended regimen.[6] The Partners PrEP trial, carried out amongst 4758 heterosexual serodiscordant couples in Uganda and Kenya, showed a risk reduction of HIV transmission of 84% in men and 66% in women taking Truvada.[7] The Botswanan TDF2 trial, which enrolled 1219 heterosexual men and women, showed an overall efficacy of 62%.[8] There is some evidence to suggest that PrEP is cost-effective, especially when compared to the high healthcare costs incurred in lifelong HIV treatment for those who are infected,[9] however, more research is needed in this area.

Numerous concerns have surfaced since the introduction of PrEP, including the development of genotypic and phenotypic resistance to TDF and FTC, which are also widely used for HIV treatment; and the concern of risk compensation, where individuals on PrEP may behave more riskily due to the misconceptions of immunity proffered by PrEP. While worrying, these have not been borne out by the evidence.

In the Partners PrEP trial, drug resistance was detected in only 1 of 3 individuals taking Truvada who became HIV-infected during the study period; no resistant virus was detected in the 33 participants of both sexes who seroconverted after enrolment in the TDF2 trial.[7,8] A meta-analysis of 6 large randomised trials failed to find a statistically significant increased risk of developing TDF resistance in subjects who seroconverted following randomisation to PrEP in their respective studies.[10] With regard to risk compensation, the same meta-analysis found no reduction in the reported use of condoms in sex amongst study participants enrolled. The number of sexual partners reported by study subjects was also not found to be higher following enrolment. The incidence of non-HIV sexually transmitted infections (STIs) has been found to be high in a number of PrEP studies—however, this may not necessarily point to increased risk-taking behaviour as pre-implementation STI rates were often not determined. The incidence of bacterial STIs like gonorrhoea and syphilis have shown a rising trend in recent years, and further emphasises the need for effective biomedical prevention of HIV transmission in light of shifts in sexual risk behaviour

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in at-risk populations. Modelling studies suggest that without PrEP, HIV incidence is unlikely to decrease substantially.[11]

The success of PrEP as a means of HIV prevention is dependent on how effectively it can be implemented in the communities where it is needed. An effective PrEP delivery model includes regular monitoring for adverse drug reactions (nephropathy and reduced bone mineral density are of concern, but are uncommon in PrEP trials); regular HIV testing; STI screening and treatment; and behavioural counselling on sexual risk reduction.

Data from demonstration projects and open-label extension studies evaluating the provision of PrEP outside of clinical trial settings is needed to guide PrEP implementation. These studies, many of which are underway in both resource-rich and resource-limited settings, seek to determine the feasibility of PrEP delivery models, patient service delivery preferences (including site of provision of PrEP services), as well as barriers to and motivators of adherence to PrEP.[12]

Such studies are needed in the local setting to inform the implementation of PrEP in Singapore. PrEP is already available in several clinics and restructured hospitals, but efforts are still much needed to increase awareness and educate the public, as well as elucidate the unique care preferences of local at-risk populations. In addition, developing a system of financing PrEP for those who need it most (but who may be ill-equipped to afford it at its current price) is an important short-term goal for healthcare providers and policymakers. Such efforts, whether for research, clinical or programmatic purposes, must be multidisciplinary and involve clinicians, patient advocates, community stakeholders and representatives from healthcare leadership.

PrEP is already strongly recommended by the World Health Organisation and the United Nations Programme on HIV/AIDS (UNAIDS) as part of a holistic strategy internationally to reduce HIV infection, which includes encouraging early testing and treating, advocating safer sex practices, and an emphasis on retention in care and adherence to treatment for HIV-infected individuals.[13,14] The UNAIDS Prevention Gap Report, published in July 2016, specifically names PrEP as one of the 5 pillars of HIV prevention, alongside providing HIV prevention services to key at-risk populations and increasing condom availability.[15] Sustainable and affordable provision of PrEP in Singapore should be made a priority in the local HIV/AIDS response on the basis of its efficacy, cost-effectiveness, and synergism with existing prevention methods.

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Original Article

Detection Rate of High-Grade Cervical Neoplasia and Cost-Effectiveness of High-Risk Human Papillomavirus Genotyping with Reflex Liquid-based Cytology in Cervical Cancer Screening

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Abstract

Introduction: This study aimed to determine the prevalence of cervical intraepithelial neoplasia grade 3 or worse (≥CIN3) and cost-effectiveness of human papillomavirus (HPV) genotyping with reflex liquid-based cytology (LBC) for cervical cancer screening in Singapore. Materials and Methods: Women who were ≥25 years old and undertook co-testing with LBC and HPV-genotyping (Cobas-4800, Roche, USA) for HPV-16, HPV-18 and 12 high-risk HPV types in a single institution were studied retrospectively. A single cervical smear in ThinPrep® PreservCyt® solution (Hologic, USA) was separated for tests in independent cytology and molecular pathology laboratories. The results were reviewed by a designated gynaecologist according to institutional clinical management protocols. Those who tested positive for HPV-16 and/or HPV-18 (regardless of cytology results), cytology showing low-grade squamous intraepithelial lesions (LSIL) or high-grade SIL (HSIL), or atypical squamous cells of undetermined significance (ASCUS) with positive 12 high-risk HPV types were referred for colposcopy. Colposcopy was performed by experienced colposcopists. Cervical biopsy, either directed punch biopsies or excisional biopsy, was determined by a colposcopist. The diagnosis of ≥CIN3 was reviewed by a gynaecologic pathologist. Cost-effectiveness of HPV-based screening in terms of disease and financial burden was analysed using epidemiological, clinical and financial input data from Singapore. Results: Of 1866 women studied, 167 (8.9%) had abnormal cytology (≥ASCUS) and 171 (9.2%) tested positive for high-risk HPV. Twenty-three CIN were detected. Three of the 10 ≥CIN3 cases had negative cytology but positive HPV-16. Compared to cytology, HPV genotyping detected more ≥CIN3 (OR: 1.43). HPV+16/18 genotyping with reflex LBC was superior in terms of cost-effectiveness to LBC with reflex HPV, both for disease detection rate and cost per case of ≥CIN2 detected. Conclusion: Compared to cytology, HPV+16/18 genotyping with reflex LBC detected more ≥CIN3 and was cost-effective for cervical screening in Singapore.

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Key words: Co-Testing, Incidence trend, Mortality, Intraepithelial neoplasia, Pap smear

Introduction

In Singapore, the age-standardised incidence rate (ASR) of cervical cancer, which has been declining since 1974, was 7.0 per 100,000 from 2010 to 2014, ranking it the tenth most common cancer among women during this period.[1] The apparent rate of decline between each 5-year period was the most dramatic from 1995/1999 to 2000/2004 with 22.8%, and from 2000/2004 to 2005/2009 with 21.4%. However, this rate of decline diminished by more than half to 9.1% from 2005/2009 to 2009/2014. The lacklustre decline in the incidence of cervical cancer may be attributable to a low participation rate of cytology screening since 2004.[2,3] To sustain a continual improvement in cervical control in the short term before the impact of human papillomavirus (HPV) vaccination is seen, it would necessitate a change in screening strategy. Screening tests with good sensitivity for high-grade neoplasia, which allows for the prevention of the development of invasive disease and, on the other hand, a longer interval between screens for those with negative screening test, may overcome the limitation of screening by cytology alone.

Oncogenic or the high-risk subtypes of HPV are the necessary aetiologic agents in the development of high-grade lesions and cervical cancer. HPV deoxyribonucleic acid

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(DNA) detection offers a great potential as a screening tool for the disease. Mayrand et al reported that the sensitivity of primary HPV DNA screening for cervical intraepithelial neoplasia grade 2 (CIN2) and CIN3 was 94.6%, compared to 55.4% for cytology test.[4] Other randomised longitudinal studies in primary screening setting confirmed the superiority of HPV DNA test over cytology in the sensitivity for high-grade CIN (≥CIN2).[5-7] In longitudinal trials involving multiple rounds of screening, HPV DNA test detected more ≥CIN3 during the first round, thus allowing appropriate treatment to be performed in preventing the development of invasive disease during the interval between screens.[8-10]

The implementation of HPV DNA test in primary screening was slow because of its low specificity for ≥CIN2. The management of women who tested positive for HPV was uncertain and referral of all these women for colposcopy would lead to unnecessary tests and over-treatment of less severe lesions with low malignant potential. One approach to resolve this dilemma is to separately test for HPV-16 and HPV-18 which are, by far, the most common HPV subtypes in ≥CIN3 and invasive cervical cancer.[11-14] In this regard, the Athena trial which used a test system with outputs for HPV-16, HPV-18 and 12 other high-risk HPV types confirmed the superiority of HPV DNA test over cytology.[15] More importantly, it yielded useful clinical information on the absolute risk of ≥CIN2 and ≥CIN3 for women who tested positive for HPV-16 and HPV-18 among women whose cytology was negative. These results allowed for the development of clinical management strategy based on the detection of HPV-16 and HPV-18. The system has since been approved by the United States Food and Drug Administration (US FDA) and is recommended in guidelines for primary screening for cervical cancer.[16,17]

Cost-effectiveness is a major budgetary concern in introducing HPV DNA primary screening for cervical cancer. A study using data from the ATHENA trial reported that HPV 16/18/12 high-risk HPV test system was cost-effective in primary cervical screening in the United States of America (USA).[18] This result is encouraging but it is well recognised that cost-effectiveness is the result of a complex dynamic process involving the operating cost of the test, further investigations and treatment of abnormal results, prevalence of HPV subtypes and burden of high-grade lesions and cervical cancer in the community. It should, therefore, be assessed by individual countries before a decision is made on its implementation.

In 2013, a pilot project that co-tested with HPV+16/18 genotyping and liquid-based cytology (LBC), and performed in 2 independent laboratories for screening of cervical cancer, was introduced in our institution. The present study aimed to determine the detection rate of ≥CIN3 and cost-effectiveness of HPV+16/18 genotyping with reflex cytology for cervical cancer screening in Singapore.

Methods and Materials

This retrospective study was approved by the Institutional Review Board.

Subjects

Women 25 years or older who attended a single institution for gynaecologic services and had undertaken co-testing for cervical cancer screening were identified. Women on follow-up for prior abnormal cervical cytology and those who reported a history of treatment for CIN, cervical or other lower genital tract cancers were excluded.

Co-Testing

Each individual had a single cervical scrape taken in ThinPrep® PreservCyt® solution. In the laboratory, each sample was divided into 2 aliquots – one was for HPV DNA testing using Cobas 4800 HPV test (Roche, USA) carried out according to the manufacturer's protocol in the molecular pathology laboratory, and the second was sent to the cytology laboratory for routine LBC analysis. Each laboratory reported the results independently. The results were reviewed by a designated gynaecologist for management decision, including colposcopy referral, in accordance with the institutional protocol (Fig. 1). Colposcopy was performed by experienced gynaecologic colposcopists. The final diagnosis was based on colposcopy directed punch biopsies, or cervical tissues obtained by loop electro-excision procedure, cervical conisation or hysterectomy.

Data Collection

This study was confined to the initial round of co-testing. Data on age, cytology and HPV DNA status, referral to colposcopy and final histological diagnosis were recorded.

Data Analysis

Descriptive data were tabulated for detection rate of abnormal cytology and HPV DNA subtypes, and rate of colposcopy referral. Cross-tabulation was performed based on the detection of CIN according to cytology and HPV categories.

Cost-Effectiveness Analysis

The incremental cost-effectiveness ratio (ICER) based on cost per quality-adjusted life-year (QALY) and clinical impact were analysed with an Excel-based Markov cohort

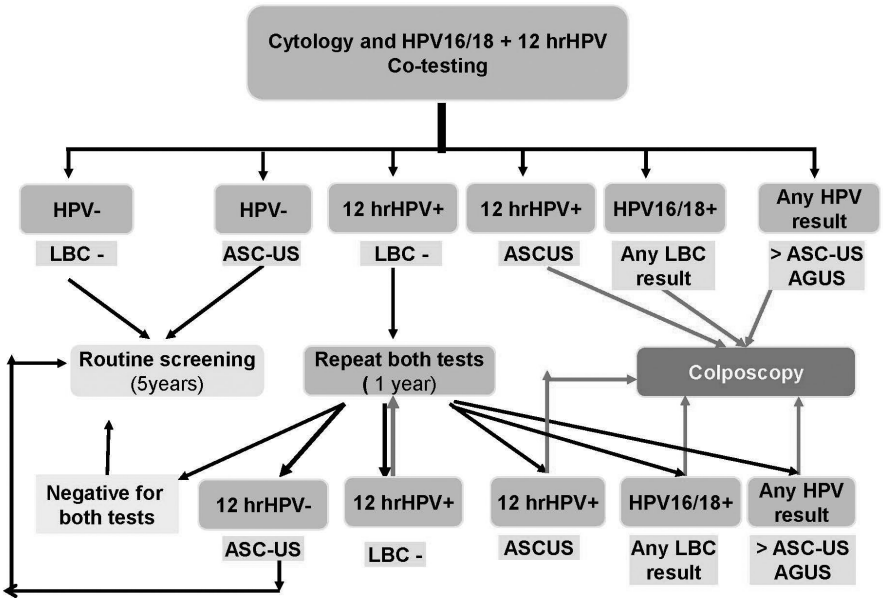

Fig. 1. A management algorithm for cervical cancer screening by co-testing.

model as described by Huh et al.[18] The model inputs were based on data derived from Singapore sources for prevalence of HPV genotypes,[19] prevalence of CIN1, CIN2, and CIN3, the cost of diagnosis and treatment of CIN and invasive cancer,[20] demography of women population and participation rate of cervical screening.[2,3] It was assumed that the non-attenders of screening were most likely to be the same individual during the screening cycles for each strategy. The sensitivity of CIN detection was based on data revealed in this current study by cytology and co-testing. The absolute details of model inputs are summarised in Table 1. For this analysis, 2 screening scenarios were compared to no screening – LBC with reflex HPV for atypical squamous cells of undetermined significance (ASCUS) and HPV+16/18 genotyping with reflex LBC for 12 high-risk HPV-positive cases.

Results

Within the study period, 1866 women, aged between 25 and 75 years, were screened by co-testing. Of 1866 co-tests, 1684 (90.2%) tested negative for intraepithelial lesion and malignancy (NILM), 167 (8.9%) were abnormal with changes of ASCUS or more severe lesions, and 171 tested positive for high-risk HPV (9.2%) (Table 2). HPV genotype distribution was 1.8% for HPV-16, 0.6% for HPV-18, and 6.8% for 12 high-risk HPV. There were 95 women who fulfilled the criteria and were called for colposcopy. By the date of this analysis, 88 (92.6%) had been examined by colposcopy and 23 women had a diagnosis of CIN on histopathology. Of the entire cohort, 10 (0.54%) cases of ≥CIN3 were detected; 7 were from women with both abnormal cytology and positive HPV tests. Three cases of ≥CIN3 had NILM and positive HPV-16; 1 of these was diagnosed as CIN3 with a focus suspicious of microinvasion (Table 3). Compared to LBC with reflex HPV, the odds ratio of detecting ≥CIN3 by HPV+16/18 with reflex LBC was 1.43 (95% CI, 0.54 to 3.77).

The health economic model analysis showed that the incidence of cervical cancer was 19.21 per 100,000 population when no screening was performed, 13.25 per 100,000 population for screen strategy of LBC with reflex HPV testing, and 6.62 per 100,000 population for strategy involving HPV+16/18 genotyping with reflex LBC. Both screening strategies were cost-effective by ICER criteria (S$2104 for LBC with reflex HPV testing and S$3623 for HPV+16/18 genotyping with reflex LBC). There was a marginal advantage in incremental net monetary benefit towards screening with HPV+16/18 genotyping with reflex LBC compared to LBC with reflex HPV testing (S$37,696 vs S$37,233, respectively [Table 4]). The one-way sensitivity test showed that sensitivity of cytology and HPV genotyping had the greatest impact on the cost-effectiveness of screening (Fig. 2). In regard to impact on disease detection compared to cytology primary screening, HPV+16/18 genotyping primary screening increased detection of invasive cervical cancer from 47.5% to 83.1% and ≥CIN2 from 56% to 80.3% respectively (Fig. 3). The number of missed and interval progression from ≥CIN2 to invasive cancer was also reduced from 20 cases per annum in cytology screening programme

Table 1. Input Data to Model for Cost-Effectiveness Analysis

Annual Progression Rate	**%**	**Annual Regression Rate**	**%**
Well to high-risk HPV	4.2	From 12 high-risk HPV/NIML to normal	58.6
12 high-risk HPV to CIN 1	8.1	From 12 high-risk HPV/LSIL to normal	45.6
12 high-risk HPV to CIN 2	0.1	From HPV16/18 with NIML to normal	43.8
12 high-risk HPV to CIN 3	0.1	From HPV16/18/LSIL to normal	21.8
16/18 to CIN 1	9.9	From CIN 1 to well	21.2
16/18 to CIN 2	0.6	From CIN 1 to HPV	2.4
16/18 to CIN 3	1.5	From CIN 2 to well	9.4
CIN 2 to CIN 3	3.2	From CIN2 to CIN 1	9.4
CIN 3 to ICC	1.1	From CIN 3 to well	3.9
		From CIN 3 to CIN 1	1.6
Prevalence of HPV/CIN/Cancer		**Test Sensitivity and Specificity**	
Prevalence of high-risk HPV	8.2	Cytology sensitivity for CIN2+	53.2
Prevalence of HPV 16/18	2.1	Cytology sensitivity for CIN3+	57.7
Prevalence of CIN 1	0.3	Specificity of cytology	73.4
Prevalence of CIN 2	0.4	HPV sensitivity for CIN2+	86.6
Prevalence of CIN 3	0.5	HPV sensitivity for CIN3+	89.9
Prevalence of ICC	0.053	HPV specificity	62.7
% Population ≥ASCUS	3.9	Colposcopy sensitivity	100
% Population Cyto+/HPV+	2.7		
Cost of Tests (2013)	**SGD ($)**	**Treatment Cost (2013)**	**SGD ($)**
Clinic visit	72.81	CIN2+	1500
Cytology screening	55.0	Cancer	25,000
HPV DNA	100		
Colposcopy/biopsy	286.14		
Screened Population		**Screening Interval**	**No. years**
Total population (women)	1,953,200	Cytology alone	3
Population ≥25 and ≤65 years old	63.7%	HPV with reflex with reflex cytology	5
% ineligible for screening	11.4	Attendance rate for managed algorithms	75%
Total eligible population	1,101,734		
Compliance rate of screening	50%		
Total screen population	550,867		

ASCUS: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial lesion; DNA: Deoxyribonucleic acid; HPV: Human papillomavirus; ICC: invasive cervical carcinoma; LSIL: Low-grade squamous intraepithelial lesion; NMIL: Negative for intraepithelial lesion or malignancy

Table 2. Cytology and HPV DNA Status of the Entire Cohort

Cytology Category	**n**	**High-Risk HPV DNA Detection**	
		n	**%**
Negative	1684	94	5.6
ASCUS	138	50	36.2
SIL	29	27	93.1
Unsatisfactory	10	0	0
Others	5	0	0
Total	1866	171	9.2

ASCUS: Atypical squamous cells of undetermined significance; DNA: Deoxyribonucleic acid; HPV: Human papillomavirus; SIL: Squamous intraepithelial lesion

Table 3. Pathological Diagnosis by Cytology and HPV Status

Cytology/HPV Status	n	No. of Colposcopy	CIN 1	CIN 2	CIN 3
SIL					
16 and/or 18 +	10	10	2	0	3
12 high-risk HPV+	17	15	3	0	2
HPV-	2	2	1	0	0
Subtotal	29	27	6	0	5
ASCUS					
HPV 16 and/or 18 +	14	13	2	0	1
12 high-risk HPV+	36	22	1	2	1
HPV-	88	5	1	0	0
Subtotal	138	40	4	2	2
Negative					
HPV 16 and/or 18 +	16	12	0	0	3
12 high-risk HPV+	78	7	1	0	0
HPV-	1590	2	0	0	0
Subtotal	1684	21	1	0	3
Overall	1866		11	2	10 (0.54%)

ASCUS: Atypical squamous cells of undetermined significance; CIN: Cervical intraepithelial lesion; HPV: Human papillomavirus; SIL: Squamous intraepithelial lesions

to 12 cases in HPV primary screening programme. Cost per person per annum for screening test and cost per case of high-grade lesion detected showed advantage towards HPV primary screening than cytology screening (Fig. 3).

Discussion

Real-world experience of primary HPV test in population screening is not yet available. We presented in this study an institutionally-based setting of cervical cancer screening which reflected the real-world individual care scenario commonly seen in places with no structured population screening programme. HPV test with types 16 and 18 genotyping was introduced to the existing practice of screening by liquid-based cytology. The rationales of the co-testing were to avoid anxiety expressed by clinicians and women towards new screening tests and to garner local laboratory and clinical experience in routine primary HPV test.

It is interesting to note the similar prevalence of abnormal test by cytology (8.9%) and HPV test (9.2%) individually. The prevalence of high-risk HPV detected was twofold higher than the rate in Singaporean women with normal cytology in a previous study, and the findings concurred with that of the ATHENA trial in the USA.[15,19] In fact, the prevalence of ≥CIN3 (0.54%) in this study was identical to that reported in the ATHENA trial. This reflected the burden of high-risk HPV and ≥CIN3 in previously screened communities in the USA and Singapore.

Of the 10 ≥CIN3 cases detected in this study, 7 had abnormal cytology and 3 had negative cytology. The increased detection rate of ≥CIN3 (OR: 1.43) was within the reported range of longitudinal clinical trials comparing primary HPV test to cytology.[8-10] One of the women with

Table 4. Comparison of Cost-Effectiveness of Different Scenarios of Screening Strategies

Screening Strategy	Strategy Characteristics	Incidence of Cervical Cancer/100,000 Women	Cost (SGD)	
			ICER	INMB
	No screening	19.21	139	
A	LBC/Reflex HPV*	13.15	2104	37233
B	LBC/HPV+ 16/18†	6.62	3623	37696

LBC: Liquid-based cytology (thin-prep); HPV: Human papillomavirus; ICER: Incremental cost-effectiveness ratio; INMB: Incremental net monetary benefit
*High-risk HPV test for ASCUS cytology.
†Cobas 4800 system (Roche).

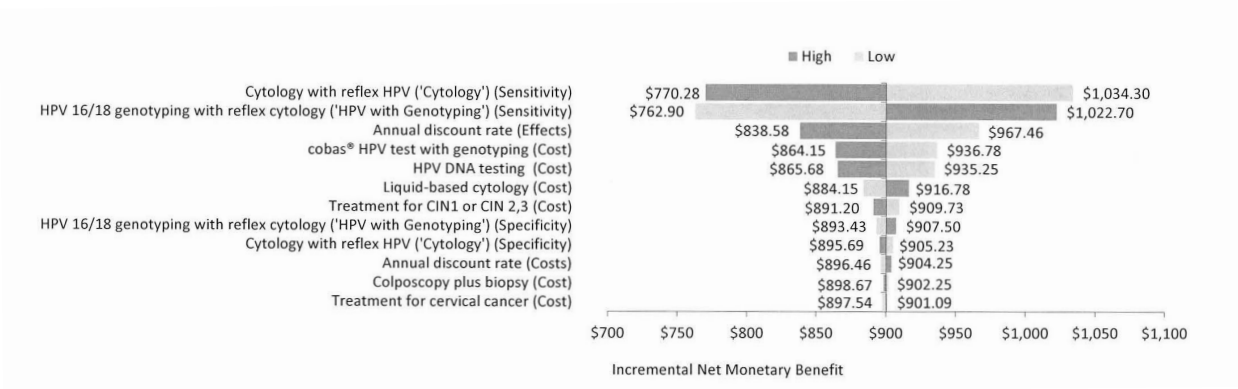

Fig. 2. A tornado diagram showing the results of a one-way sensitivity analysis.

repeated negative cytology tests was found to be positive for HPV-16 and a final diagnosis of a high-grade lesion with a focus of suspicious microinvasion highlighted the benefit of HPV test which allowed this woman's lesion to be prevented from progressing to a clinical carcinoma of the cervix during the interval of screening. This capability of HPV test at the initial round of screen was previously reported by Ronco et al in the follow-up of 4 European longitudinal studies.[21]

The fact that LBC and HPV tests were carried out in 2 independent laboratories which reported the results separately allowed us to analyse the results in this study in the manner of primary HPV test with reflex cytology. Of the 10 CIN3+ cases, 7 would have been referred for immediate colposcopy because of positive test for HPV16/18, regardless of cytology. The remaining 3 cases would have been referred for colposcopy because of squamous intraepithelial lesions (SIL) on LBC in 2 cases and ASCUS with reflex positive high-risk HPV test in 1 case. Based on the rate of concurrent positivity on cytology and HPV in this study, 4.1% (77/1688) of the women would have been referred for colposcopy, with a detection rate of ≥CIN3 in 1 out of 7.5 colposcopy referrals. This would substantially reduce the cost of screening tests without overburdening the colposcopy services.

Not surprisingly, health economic modelling has estimated a reduced incidence rate of cervical cancer with screening. More importantly, the incidence rate was lower in screening scenarios that employed HPV-based testing. Using criteria set by the World Health Organization that an ICER of onefold or less of the gross domestic product is cost-effective for medical intervention, the HPV+16/18 genotyping with reflex LBC proved to be highly cost-effective for Singapore. In terms of impact of screening on disease burden, HPV+16/18 genotyping detected more ≥CIN2 and cervical cancer compared to LBC primary screening with reflex HPV test. Our findings concurred with studies from the USA and Europe.[21-23] These findings are in distinct contrast to early studies of primary HPV screening

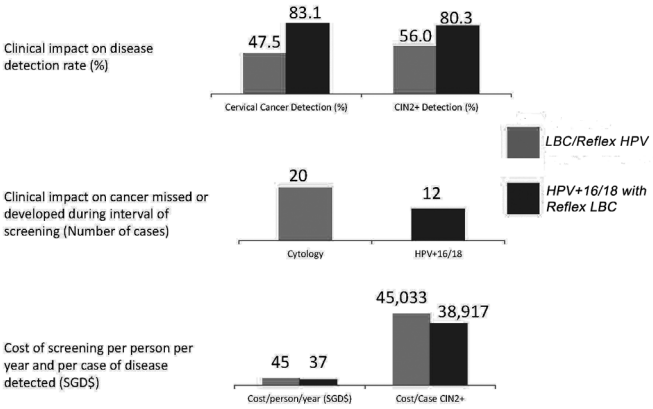

Fig. 3. Comparison of clinical and monetary cost of 2 screening strategies.

without cytology triage as HPV test has low specificity for high-grade lesions.[24]

Because of the extension in screening interval from 3 years for cytology screening to 5 years for HPV-based screening, the net monetary savings in the cost of screening per person per year and costs of detecting ≥CIN2 per case were lower for HPV-based screening. It is envisaged that (as shown in clinical trials in population screening) when subsequent rounds of screening detect fewer HPV-positive cases and ≥CIN3, the number of reflex cytology tests would also substantially diminish.[21,25] This would translate to further financial cost savings and improve the margin of cost-effectiveness in a sustained long-term screening programme.

Conclusion

The findings of the present study corroborated the reported results of clinical trials that HPV-based cervical screening is superior to cytology screening. In Singapore, HPV+16/18 genotyping with reflex LBC detected more ≥CIN3 and was highly cost-effective.

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Original Article

An Audit of 829 Paediatric Epidurals in a Tertiary Singapore Hospital: Complications and Conundrums

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Abstract

Introduction: The incidence of complications related to epidural analgesia remains less well defined in the paediatric population as compared to adults. A retrospective review of prospectively collected data was performed to review and quantify risks of both adverse events and complications related to epidural analgesia in our Singaporean paediatric population. Materials and Methods: Data from the Acute Pain Service (APS) was prospectively collected over 19 years. Details included the age of the patients, level of insertion of the epidural catheter, number of attempts, staff grade of the practitioner, adverse events and complications. Results: Collectively, 829 epidurals were performed from 1 June 1997 to 31 May 2016. No deaths or major complications occurred within the 16-year period. There were 5 instances of dural puncture (0.6%). The incidence of minor postoperative complications was 3.1% with the majority of postoperative events comprising catheter-related problems (n = 161, 22.4%). Prolonged use of the catheter beyond 3 days is associated with a statistically significant increase in the frequency of skin infective/ inflammatory changes (P <0.01). We highlight common complications and conundrums faced. Conclusion: Epidural analgesia has been shown to be associated with a relatively low risk of complications both in the adult and paediatric populations, albeit with a fourfold increased risk in the latter cohort. Adverse events reported are largely related to catheter problems and have minimal impact upon the patient.

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Key words: Anaesthesia, Analgesia, Child, Post-dural puncture headache

Introduction

Providing excellent paediatric epidural analgesia remains a challenge to the anaesthetist, not least due to the technical difficulties inherent in managing patients with weight disparities (ranging from 2.5 kg or less to an excess of 100 kg), the myriad variables in prescription (from additives used to dosing limits), as well as the risk of missing subtle signs of local anaesthetic toxicity in the non-verbal child.

Of all the potential adverse events, major permanent neurological complications are amongst the most devastating. "Awake epidurals" are recommended routinely in adults (in order to minimise the risk of neurological injury) but are impractical and precluded in young children, particularly those less than 6 years old, wherein the alternative option of patient-controlled analgesia (PCA) may not be feasible.

Recent adult data from 707,455 central neuraxial blocks (CNBs) in the United Kingdom estimates the risk of permanent neurological injury from CNBs at 2.0-4.2/100,000 (estimated 0.002% to 0.004%), with risk of paraplegia or death ranging from 0.7-1.8/100,000 (0.0007% to 0.0018%).[1] Data on paediatric CNBs, whilst not amounting to a population size of 16,000[2,3,4] have shown epidural analgesia to be safe but with a higher complication rate (up to 7 times that in adults). There is consistent evidence of a significantly higher morbidity risk associated with paediatric CNBs, approximately 1.5/1000[5] which is about 6 times of that associated with peripheral nerve blocks (PNBs), and complications are 4 times more likely to occur in those younger than 6 months of age.[6] Consequently, there has been a global increase in the use of PNBs and a decline in CNBs to optimise postoperative analgesia in both the adult and paediatric populations.

Some variation exists in the incidence of complications between the different international populations studied. Direct comparisons are difficult because of complexities

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and variations in their classification. Recent studies have predominantly been conducted in Caucasian populations, but there remains a paucity of large data audits in the Asian population. We aimed to both quantitatively and qualitatively review the risks of adverse events and complications related to epidural analgesia in Singapore's multi-ethnic paediatric population.

Materials and Methods

Since its inception in 1997, the Department of Paediatric Anaesthesia has prospectively followed up every epidural performed as part of its Acute Pain Service (APS) audit. Data documented in the APS forms include patient demographics, surgery performed, level of epidural catheter placement, technical/procedural challenges and problems encountered, prescription, quality of pain relief and subsequent modifications, including plans for alternative analgesia. Initial data is entered by the anaesthetist who inserted the epidural. The APS team follows up patients at least twice a day, up to and including 24 hours after catheter removal or until all issues related to the epidural have been resolved.

Analgesic quality is regularly assessed by way of frequent pain assessment using age-appropriate scores. Observational information (e.g. impact on sleep/rest cycle, mood, social interaction and activity) is integrated with these scores and inform subsequent management. Mandatory examinations include daily inspections for evidence of catheter site complications, catheter migration, neurological deficits, evidence of infection and other cardiorespiratory complications. Adjustments in epidural drug concentration and rate of infusion, as well as the use of analgesic adjuncts are also noted. Any complications or adverse events are recorded and followed up until their resolution.

The prospective data was then retrospectively reviewed for the incidence of complications and adverse events. Our review included all children on epidural catheters from 1 June 1997 to 31 May 2016 and encompassed thoracic, lumbar, trans-sacral and caudal approaches. Single shot caudal epidurals were excluded. Patients were subdivided into the following age groups: a) neonates <28 days old, b) infants <1 year old, c) toddlers 1 to 2 years of age, d) preschoolers 3 to 6 years of age, e) children 7 to 12 years of age, and f) adolescents >12 years of age.

Data on all minor problems related to the epidurals, adverse events and complications were collected. Complications were divided into intraoperative (procedural) and postoperative events and incidents were graded in severity. Where significant complications were identified, the medical records of the patient were traced to obtain further details about the presentation as well as the progress until resolution.

Classification of Incidents

Grades 1 to 3 describe complications/serious events while Grade 4 describes adverse/undesirable events with no patient harm or sequelae:[2]

- Grade 1: Any life threatening event or any complication resulting in permanent deficit (e.g. permanent neurological deficit; meningism/epidural abscess; serious cardiac or respiratory event).

- Grade 2: Resolved with intervention (e.g. neurological damage with late recovery [up to 1 year]; deep infection requiring surgical intervention).

- Grade 3: Resolved with minimal/no intervention (e.g. transient neurological symptoms with recovery by the time of discharge; transient cardiac/respiratory events; local infection requiring antibiotics).

- Grade 4: Adverse effects with no sequelae (e.g. local skin inflammation resolving spontaneously without intervention, within 24 hours of catheter removal; recognised dural and vascular punctures; unilateral/inadequate block; failed block).

Statistical analysis was undertaken using IBM SPSS Statistics version 20.

Results

Demographics

A total of 829 epidurals were performed (Table 1). Mean duration that the epidural catheter was left in situ was 2.3 days, with a range of 0 to 6 days (95% confidence interval [CI], 2.21 to 2.35).

Complication Rate

A total of 334 events were recorded, ranging from mild catheter-related problems to complications requiring medical attention (Table 2). These were divided into procedure-related events (n = 53) and postoperative events (n = 281) (Fig. 1). Cases with more than 1 complication or adverse event were counted twice.

Procedure-related Events (n = 53)

There were 53 separate intraoperative events (6.4%) which occurred in 52 children (Table 3) (Fig. 2). There were 5 instances of dural puncture (0.6%). Four incidents of dural puncture were recognised at the time of insertion of the Tuohy needle. In each case, the Tuohy needle was removed and the epidural successfully re-sited. In the fifth case, a suspicion of a miniscule fluid leak was observed insufficient to assay and distinguish from residual-aspirated saline used for loss of resistance. This persisted after the catheter was inserted and in view of a possible dural tap, no drugs were given via the epidural catheter, which was

Table 1. Patient Demographics

Gender	n	%	Weight	(Kg)
Male	476	57.4	Mean	19.6 (95% CI 18.63 – 2062)
Female	353	42.6	Range	2.5 – 108
Age		**n**		**%**
Neonates <28 days		15		1.8
Infants, 1 – 12 months		115		13.9
Toddlers,1 – 2 years		191		23.0
Pre-schoolers, 3 – 6 years		229		27.6
Child, 7 – 12 years		195		23.5
Adolescent, >12 years		84		10.1
Segmental Approach		**n**		**%**
Thoracic		311		37.5
Lumbar		432		52.1
Sacral		51		6.2
Caudal		35		4.2
Proceduralist		**n**		**%**
Specialist/Consultant		615		74.2
Trainee		214		25.8
Epidural Drugs		**n**		**%**
Local anaesthetic used				
Bupivacaine		803		96.9
Levo-bupivacaine		25		3
Ropivacaine		1		0.1
Additive used				
None		117		14.1
Fentanyl		664		80.1
Morphine		19		2.3
Clonidine		29		3.5

Table 2.Complications by Level and Age Group

Age Group	No. of Epidurals	No. of Patients with Procedure-related Complications (%)	No. of Patients with Postop Complications
Neonate, <28 days			
Thoracic	1	1 (100.0)	1 (100.0)
Lumbar	8	0 (0)	3 (37.5)
Caudal	6	0 (0)	3 (50.0)
Total	15	1 (6.7)	7 (46.7)
Infant, 1 – 12 months			
Thoracic	30	3 (10.0)	6 (20.0)
Lumbar	61	4 (6.6)	25 (40.9)
Sacral	12	1 (8.3)	4 (33.3)
Caudal	12	1 (8.3)	3 (25.0)
Total	115	9 (7.8)	38 (33.0)
Toddler, 1 – 2 years			
Thoracic	64	6 (9.4)	21 (32.8)
Lumbar	94	7 (7.4)	19 (20.2)
Sacral	27	3 (11.1)	10 (37.0)
Caudal	6	0 (0)	2 (33.3)
Total	191	13 (6.8)	52 (27.2)
Preschooler, 3 – 6 years			
Thoracic	107	8 (7.5)	32 (29.9)
Lumbar	105	8 (7.6)	34 (32.4)
Sacral	10	0 (0)	2 (20.0)
Caudal	7	1 (14.3)	2 (28.6)
Total	229	16 (7.0)	70 (30.6)
School-going children, 7 – 12 years			
Thoracic	71	0 (0)	29 (40.8)
Lumbar	118	3 (2.5)	34 (28.8)
Sacral	2	0 (0)	0 (0)
Caudal	4	0 (0)	0 (0)
Total	195	3 (1.5)	63 (32.3)
Adolescent, >12 years			
Thoracic	38	1 (2.6)	9 (23.7)
Lumbar	46	5 (10.9)	10 (21.7)
Total	84	6 (7.1)	19 (22.6)
Total			
Thoracic	311	19 (6.1)	98 (31.5)
Lumbar	432	27 (6.3)	124 (28.7)
Sacral	51	4 (7.8)	16 (31.4)
Caudal	35	2 (5.7)	10 (28.6)
Total	829	52 (6.3)	249 (30.0)

then removed postoperatively.

None of the cases resulted in an inadvertent spinal block or high block. Subsequent to the dural puncture, none of the affected children developed a postdural puncture headache.

Of note, 4 out of the 5 cases of dural tap occurred in younger children <6 years of age who presented technically more challenging procedures requiring more than 2 attempts to eventually identify the epidural space. Three were lumbar epidurals and 2 were thoracic epidurals. All 5 cases were performed by a specialist paediatric anaesthetist.

Postoperative Events (n = 281)

There were a total of 281 postoperative events (33.9%) occurring in 249 children (Table 3) (Fig. 3). Our study revealed no major complications (grades 1 or 2).

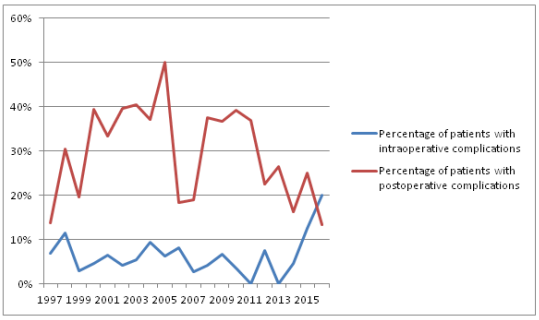

Fig. 1. Chart showing the incidence of intraoperative and postoperative events among all epidurals done per year.

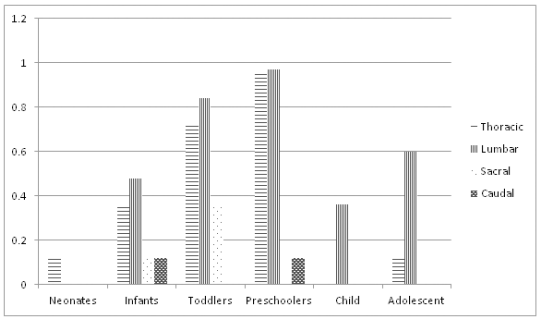

Fig. 2. Chart showing the percentage of intraoperative events out of all epidurals.

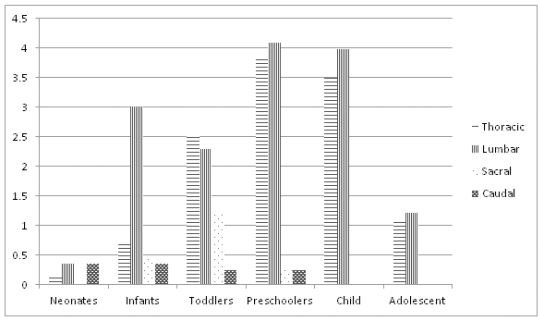

Fig. 3. Chart showing the percentage of postoperative events out of all epidurals.

Table 3. Incidence of Individual Complications

Procedure-related Complications	**Incidence**	**% of Total Epidurals (95% Confidence Interval)**
Vascular puncture	33	4.0 (2.85 – 5.54)
Inability to thread catheter	10	1.2 (0.66 – 2.21)
Dural puncture	5	0.6 (0.26 – 1.40)
Failed insertion	5	0.6 (0.26 – 1.40)
Total	53	6.4 (4.92 – 8.27)
Postoperative Complications	**Incidence**	**% of Total Epidurals (95% Confidence Interval)**
Catheter-related		
Leak	55	6.6 (5.13 – 8.54)
Slipped out	73	8.8 (7.06 – 10.9)
Disconnected	21	2.5 (1.66 – 3.84)
Contaminated	11	1.3 (0.74 – 2.36)
Kinked	8	1.0 (0.49 – 1.89)
Occluded	8	1.0 (0.49 – 1.89)
Total	176	21.2 (18.58 – 24.14)
Skin inflammation	39	4.7 (3.46 – 6.37)
Unilateral/inadequate/ excessive motor block	35	4.2 (3.05 – 5.82)
Neurological	19	2.3 (1.47 – 3.55)
Back pain	4	0.5 (0.19 – 1.23)
Cardiovascular	4	0.5 (0.19 – 1.23)
Respiratory	1	0.1 (0.02 – 0.68)
Local anaesthetic toxicity	3	0.4 (0.01 – 1.1)
Total	281	33.9 (30.75 – 37.19)

Grade 3 Complications

There were 27 (3.3%) (95% CI, 2.3% to 4.7%) minor/Grade 3 complications, including 19 transient neurological symptoms, 4 cardiovascular events, 1 respiratory event and 3 possible cases of local anaesthetic (LA) toxicity. The cases of LA toxicity and respiratory compromise were likely concurrent events not directly attributable to the use of an epidural catheter.

1) Transient Neurological Symptoms (2.3%)

Nineteen children experienced transient neurological symptoms with the epidural catheter still in situ. Of these, 14 occurred in lumbar, 3 in thoracic, 1 in sacral and 1 in caudal epidurals. These cases required catheter removal as neurological symptoms did not abate after the withdrawal of a short segment of the epidural catheter or reduction in the concentration or rate of local anaesthetic infusion. The symptoms mostly involved unilateral lower limb weakness. One patient suffered right foot parasthesia (0.1%). All cases, however, resolved within 48 hours of removal of the epidural catheter with no permanent neurological sequelae.

2) Cardiovascular Events (0.5%)

This was defined as any abnormalities in cardiovascular parameters such as heart rate, rhythm or systemic blood pressure. Four children evinced adverse cardiovascular events, of which 2 manifested bradycardia and 2 developed hypotension (Table 4). Of the 2 cases of bradycardia, 1 was attributed to epidural fentanyl and another was found to be unrelated to the epidural. Of the 2 cases of hypotension, 1 was due to postoperative hypovolaemia and the second was related to the systemic vasodilatory effects of the epidural LA.

Table 4. Logistic Regression of Factors Predicting Procedure-related and Postoperative Complications

Factors Affecting Procedure-related Complications	**Odds Ratio**	***P* Value**
Number of attempts*	**4.1**	**0.00**
Involvement of trainee	**1.4**	**0.36**
Age group of child†	**0.8**	**0.11**
Segmental approach of epidural‡	**1.0**	**0.84**
Factors Affecting Postoperative Complications	**Odds Ratio**	***P* Value**
Number of attempts*	1.2	0.51
Involvement of trainee	0.9	0.69
Age group of child†	0.9	0.28
Segmental approach of epidural‡	0.9	0.47

*Number of attempts: ≤2 or >2.
†Age group of child: neonates <28 days old; infants <1 year old, toddlers 1-2 years old, preschoolers 3-6 years old, children 7-12 years old and adolescents >12 years old.
‡Segmental approach of epidural: thoracic, lumbar, sacral and caudal.

3) Concurrent Respiratory Event

This was found to be the result of a lung collapse/consolidation following thoracotomy and lung resection (it was unrelated to the epidural infusion).

4) Possible LA Toxicity

i) Cardiovascular event – A neonate was administered bupivacaine at an inadvertently high infusion rate, but manifested only relative bradycardia in the range of 100-110 beats/minute coupled with somnolence; ii) Respiratory event: A transient episode of apnea and cyanosis occurred in a 1-month-old infant. This was felt to be more likely due to postoperative apnea or breath holding; iii) Neurological event: A 3-year-old remained uncharacteristically very drowsy, apathetic and sweaty even 8 hours after the general anaesthesia, which was possibly related to the epidural infusion.

Grade 4 Complications

There were a total of 254 grade 4 events (30.6%). The majority of postoperative events consisted of catheter-related problems (n = 176, 21.2%). The most common of these were catheters that had dislodged or slipped out (n = 73).

Thirty-nine postoperative events were cases of transient localised skin inflammation (4.7%). This usually consisted of superficial skin erythema over the epidural site. Of these, 7 patients were found to have a small pustule at the epidural site (0.8%). There were no other features of infection such as tenderness and warmth over the skin. One patient was found to have a yellowish discharge from the epidural site which was sent for culture. Although moderate growth of *Acinetobacter baumanii* was found, the patient remained clinically well and asymptomatic and all evidence of infection/inflammation resolved within 24 hours without any antibiotic therapy. This suggested colonisation rather than an infection. All cases resolved spontaneously without antibiotics within 24 hours of catheter removal. There were no cases of meningism, abscess or deep infection.

There were 35 cases (4.2%) of Grade 4 neurological symptoms responding to simple interventions such as withdrawal of the epidural catheter or change in the concentration or rate of local anaesthetic infusion, and did not require removal of the epidural catheter. The patients presented with symptoms such as unilateral block, excessive motor block and inadequate/patchy block.

Analysis of Factors Contributing to Complications

We conducted a logistic regression analysis to try to predict procedural and postoperative complications using number of attempts (≤2 or >2), involvement of trainee, age group, and level of epidural as predictors. Only the number of attempts was statistically significant, indicating that it is a reliable predictor of procedural complications ($P<0.001$). The odds ratio is 4.1 if the number of attempts exceeds 2.

None of these factors were shown to have a statistically significant effect on the rate of postoperative complications. Compared to short-term use (≤3 days), prolonged use of the catheter beyond 3 days is associated with a statistically significant increase in the frequency of skin infective/inflammatory changes (odds ratio 4.5, $P<0.001$). We found no significant difference between the rate of infections in caudal catheters compared with catheters placed at other levels.

In our institution, most paediatric epidurals are inserted by consultant specialist anaesthetists (Table 5). Trainees insert a smaller percentage of epidurals in children aged below 3 years. Of these, 83% were sited in the lumbar levels. Trainees performed 33% of lumbar epidurals in children of all ages.

Discussion

We demonstrated a fall in the overall incidence of paediatric epidural analgesia over the last 19 years, which is consistent with international data. It mirrors an increasing preference for peripheral nerve blocks, which are known and documented to have a superior safety profile.[6,7] Most of the complications documented in our audit occurred in the postoperative period. Regression analysis revealed no statistically significant factors associated with postoperative complications in general. This is in contrast to the other studies done internationally, which demonstrates a higher

Table 5. Anaesthetists Performing the Epidurals

Age Group	Anaesthetist Performing the Epidural (% of Total)		
	Specialists	Trainees	Total
Neonate	13 (87%)	2 (13%)	15
Infant	102 (89%)	13 (11%)	115
Toddler	153 (80%)	38 (20%)	191
Preschooler	164 (72%)	65 (28%)	229
Child	124 (64%)	71 (36%)	195
Adolescent	59 (70%)	25 (30%)	84
Total	615 (74%)	214 (26%)	829

incidence of complications in infants compared to older children.[2,6]

Previous studies have demonstrated an increased risk of neurological complications in children even when compared to epidurals performed in anaesthetised adults.[2-4,6] The incidence of complications of paediatric epidurals is known to range from 29 in 10,000[6] to 76 in 10,000[3], with an overall risk of 0.66% (95% CI, 0.6% to 0.7%).[8] In comparison, a study done on anaesthetised adults found an incidence of approximately 14 in 10,000 of neurological symptoms, all of which were subsequently found to be unrelated to the epidural catheter.[9]

Sensations of paraesthesia or pain upon epidural bolus injection are key clinical indicators associated with an increased risk of postoperative neurological complications.[10] This feedback, whilst valuable in awake adult patients, is lacking in most paediatric patients who are already anaesthetised or deeply sedated during epidural insertion. There is no demonstrable increased risk of neurological complications when regional anaesthesia is performed under general anaesthesia in children,[11] as is our practice in the majority of cases. Our study revealed no major complications over 19 years (95% CI, 0% to 0.46%) and this is consistent with the very low rate of complications also found by other similar studies,[2-4] but may not be a true reflection of incidence due to the relatively small population size.

Our overall incidence of dural puncture was 0.6%, which is comparable with the PRAN study (0.9%). Published data suggests an incidence of 0.05% of postdural puncture headache (PDPH) after epidural analgesia.[2] We found no cases of PDPH, which may be due in part to a small sample size, or under-reporting by children who were not able to communicate their symptoms.

The incidence of minor or Grade 3 complications (27 patients, 3.3%) is comparable to similar studies done abroad.[4] There were 19 cases of transient neurological symptoms necessitating catheter removal, all of which recovered within 24 hours. Although the risk of transient neurological symptoms was higher than that of other studies,[2,6] none of our patients suffered prolonged neurological deficits beyond 24 hours.

The incidence of hypotension was 0.36%, comparable to that found by the PRAN.[4] Two out of 3 episodes of hypotension occurred in children with thoracic epidurals, which is in keeping with the findings by the PRAN in which 6 out of 7 cases of hypotension occurred with thoracic epidurals.

While our incidence of major complications is low, our incidence of adverse events appears to be higher than in previous studies done in predominantly Caucasian populations. A plausible reason for this difference may lie in our definition of adverse events, which includes a broader definition of catheter-related problems, encompassing even the cases where the event (e.g. leaking catheter) did not result in any deleterious effect on the patient. A similarly broad definition was used in a 1994 Canadian study showing a 67% incidence of side effects and complications.[10]

Of the adverse events, 39 (4.7%) were cases of transient localised skin inflammation resolving spontaneously without requiring antibiotics. There were no cases of severe infections such as meningism or deep infection. Our results are consistent with other studies previously reporting a very low incidence of infection after epidural catheters used for postoperative analgesia.[12] A Boston study on epidural catheter-associated infections in children identified a 0.12% incidence of infections.[13] Of these cases, epidural catheters inserted for the management of chronic pain were associated with a significantly higher risk of infection compared to those inserted for postoperative pain, which occurred only in immunosuppressed children.

Further analysis revealed a statistically significant increase in the rate of skin inflammation in catheters kept beyond 3 days. This supports our preferred policy to remove epidural catheters within 72 hours of placement as a routine (unless special indications dictate otherwise) so as to minimise the risk of infection. Similar results were demonstrated in previous studies, which showed that the rate of infection was increased with prolonged duration of epidural catheterisation.[13]

Caudal catheters appear to present no demonstrably increased risk of infection, a finding corroborated by our own audit.[2] This is in spite of a potential for bacterial colonisation from faecal soilage of caudal catheters, especially since caudal catheters are more commonly used among younger children who are not yet toilet trained.[12] We (the authors) prefer the utilisation of the trans-sacral approach to a caudal epidural as opposed to the traditional more caudad approach

via the sacral hiatus, simply because this allows secure transfixation of the epidural catheter at a distance that is further removed from the anus and similarly further from potential faecal contamination. This approach is not ubiquitously taught in all paediatric anaesthetic centres and varies with regional practice as well as the anaesthetist's preference or familiarity. Its use is further limited to patients 8 years and younger, before complete sacral ossification occurs.

The majority of postoperative events consisted of catheter-related problems, most commonly dislodgements or migrations, followed by leaks around the epidural site. Catheter-related problems may predispose to premature termination of epidural analgesia[4,10] and in adults, these can in fact account for 12% of premature terminations of epidural analgesia.[9] The frequency of leakage around the epidural has been reported to be 15%.[14] An obvious predisposing cause of this is that the epidural catheters are inserted through the Tuohy needles, and are of smaller diameter. In our study, 18-19G Tuohy needles were used with 20-23G catheters. A larger difference in size between the needle and catheter may predispose the patient to a greater leakage around the catheter site. This may compromise the integrity/sterility of the dressing and contribute to catheter dislodgement and/or contamination. Proactive attempts at addressing this problem include utilising topical skin adhesives at the insertion site to seal the leak and implementation of mandatory inspection and redressing the epidural site with sterile occlusive dressings when required, before reversing and extubating the patient. Other common problems include disconnection of the catheter from the filter and contamination of the epidural catheter, usually due to the inadvertent removal of the dressing. Sacral and lumbar catheters were the most likely to slip out, accounting respectively for 15.8% and 9.3% of problems at that level. This is in contrast to the PRAN study which showed a higher incidence of catheter-related problems at the thoracic level.[4]

Drug errors have been found in other studies to have an incidence of 10-13:10,000.[2-4] There was only 1 documented drug error in our study (0.1%), which may reflect either safe and effective drug administration systems both in the operating rooms and in the wards, or under-reporting. With the commencement of pain incident reporting in 2014 as part of the APS audit, further regulatory measures were introduced to promote a culture of quality, safety and communication via intra- and inter-departmental discussions and incident reporting to effect the necessary changes and improvements.

In view of the higher complication rates and risks involved in neonatal and young infant regionals, we recommend that these epidurals be inserted by consultant specialist anaesthetists. Close supervision of senior trainees or junior staff is mandatory. Since neither experience nor training preclude the incident of an inadvertent dural tap, senior staff should maintain vigilance at all times. Senior staff need to consciously incorporate epidural analgesia (where applicable) in their practice and whilst it is inspiring to teach, the practical balance of risks versus benefits to both patient and staff members should also be carefully considered and not marginalised.

The lack of serious morbidity in our series should not encourage complacency but drive a heightened sense of responsibility to prevent any such occurrence. Strict protocols, vigilant monitoring and follow-up as well as consultant grade supervision are all important measures to maintain safety standards and quality assurance. Expedient management with attentive supervision by senior staff may avert potentially serious or permanent sequelae and optimise pain control, particularly in the less than perfectly working epidural.

Although our collection of 829 cases is modest in comparison to international data, it mirrors similar practice trends and morbidities encountered globally. It is the first comprehensive local audit and represents an Asian, as opposed to a largely Caucasian, population. This allows a review of our past and current safety standards and practice. We acknowledge that practices may have changed over the course of the 19 years of data collection. Regular departmental review of adverse events in the past may have given rise to safer practices.

However, our study was subject to several limitations. Firstly, the small sample size may have resulted in a falsely reassuring incidence of major complications. Secondly, being a retrospective study, specific details were not available. These included details on preparation and cleaning, use of perioperative antibiotics, and the number of years of experience of the operator. Thirdly, the study was limited to a single institution, whose practices and conclusions may not be readily extrapolated to a wider population. Finally, whilst the subsequent follow-up of postoperative events were done by a team of doctors, the details of epidural insertion and intraoperative events were self-reported, possibly affecting the true rate of events.

Conclusion

Both international and local data support evidence that epidural analgesia is largely safe in the paediatric population. Adverse effects incurred are largely minor ones resulting in minimal or no long-standing sequelae, such as catheter-related complications, cutaneous inflammatory changes at insertion site and transient neurological symptoms. However, there remains a small risk of serious, long-lasting and potentially devastating adverse events.

Advocates of paediatric epidurals stand correct in extolling the advantages of superior postoperative analgesia and the relatively low risk of complications. However, if there is a viable option of PNB over CNB, the ideal choice would be the former in terms of risk-benefit.[6]

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Original Article

Routine Staging Using Chest Computed Tomography in Workup of Treatment-Naïve Hepatocellular Carcinoma Prior to Locoregional Therapy: Is There a Need?

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Abstract

Introduction: The lung is the most common site of distal metastasis in patients with hepatocellular carcinoma (HCC), as seen in more than half of patients with extrahepatic disease. The incidence of pulmonary metastasis in all patients with HCC, however, remains low (between 4.5% to 20%). Their presence, nevertheless, contraindicates curative locoregional therapies. The role of staging chest computed tomography (CT) before locoregional treatment is not well defined. This study aimed to assess the utility of pre-treatment chest CT prior to locoregional therapy. Materials and Methods: Retrospective review of continuous cases of treatment-naïve HCC referred for locoregional therapy from 2004 to 2013 was performed. Patients with pre-treatment chest CT were evaluated for the presence of pulmonary metastases. HCC features (size, numbers, vascular invasion, nodal status and bone metastases) were recorded. Univariate analysis and multivariate logistic regression were performed for significant association. Results: A total of 780 patients were reviewed, of which 135 received staging chest CT. Pulmonary metastases (n = 17, 12.6%), benign lesions (n = 41, 30.4%) and indeterminate lesions (n = 11, 8.1%) were detected. Among the indeterminate lesions, there were losses to follow-up (n = 2) and deaths within the study period (n = 3). All patients with pulmonary metastases were declined locoregional therapy. Univariate analysis showed statistical significant association between pulmonary metastases with the number of intrahepatic lesions (*P* <0.01), primary tumour size (*P* = 0.018) and presence of vascular invasion (*P* <0.01). On multivariate analysis, the number of intrahepatic lesions (OR: 9.7; 95% CI, 1.6 to 57.2; *P* = 0.012) and presence of both hepatic and portal venous invasions (OR: 11.8; 95% CI, 1.1 to 128.8; *P* = 0.043) were the 2 independent positive predictors of pulmonary metastases. Conclusion: The prevalence of pulmonary metastasis is low in HCC and our study does not support the routine use of staging chest CT in all treatment-naïve patients. It can, however, be considered in cases with multiple lesions or vascular invasion.

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Key words: Metastasis, Liver, Lung

Introduction

Hepatocellular carcinoma (HCC) is the most common primary tumour of the liver. It is a major health issue, being the fifth most common tumour in the world with an increasing incidence.[1] Despite advances in treatment, it remains a disease with poor prognosis and survival.[2] The incidence of hepatocellular carcinoma is highest in Asia and Africa due to the high prevalence of hepatitis B and C infections and related liver disease.[3,4]

Staging systems are key to prognostication and treatment choice in newly diagnosed HCC. To this end, several staging systems have been proposed, of which the Barcelona Clinic Liver Cancer (BCLC) staging is the most commonly used classification in the Western world. Broadly, surgical resection and locoregional treatment (LRT) such as percutaneous ablation and transarterial chemoembolisation confer the best survival outcome for patients with early and intermediate stage disease, with systemic chemotherapy (sorafenib) reserved for advanced stage disease characterised by extrahepatic metastasis.[5-8]

The lung is the most frequent site for HCC metastasis,[9] as seen in more than half of patients with extrahepatic disease.[10]

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Table 1. Association between Pulmonary Metastases and the Size of Intrahepatic Lesions

	Maximum Primary Tumour Diameter			Total
	<5 cm	5 cm to 10 cm	>10 cm	
Benign or no lung lesions	37	30	40	107
Lung metastases	1	4	12	17
Total	38	34	52	124

P value from Fisher's exact test <0.018.

Table 2. Association between Pulmonary Metastases with Increased Number of Intrahepatic Lesions

	Number of Intrahepatic Lesions			Total
	1	2 to 3	>3	
Benign or no lung lesions	65	19	23	107
Lung metastases	2	7	8	17
Total	67	26	31	124

P value from Fisher's exact test <0.018.

The prevalence of pulmonary metastasis in HCC patients, however, is low (between 4.5% to 20%).[10-12] The presence of lung metastasis excludes patients for curative LRT.[5-8] While the value of routine staging chest computed tomography (CT) prior to curative treatment in other common cancers such as colorectal cancer have been well described,[13-16] to date, however, the clinical benefit of a routine staging chest CT for exclusion of metastasis prior to commencement of LRT in HCC remains to be systematically studied.[17] This study aims to assess the value (if any) for routine pre-treatment chest CT in treatment-naïve patients with HCC prior to LRT and identify any potential predictors for lung metastasis based on tumour morphology.

Materials and Methods

A retrospective study involving consecutive cases of treatment-naïve HCC from our institution's HCC registry between 2004 and 2013 was performed. This study was approved by our institutional review board and waiver of informed consent was obtained.

Cases identified from our registry were diagnosed based on either histology or imaging criteria according to the American Association for the Study of Liver Diseases (AASLD) practice guidelines.[18] Patients with newly diagnosed HCC who received pre-treatment chest CT were included in our study and their initial chest and abdomen CT scans were reviewed by 2 consultant radiologists, each with at least 8 years of experience in body imaging. Patients who did not receive pre-treatment chest CT were excluded from further analysis. The chest CT studies were performed based on a combined tumour board decision, typically for intermediate and advanced staged tumours, and all studies were performed for exclusion of lung metastases prior to LRT. The CT scans were performed with either Siemen's Somatom Definition AS 128-slice or Siemen's Somatom Sensation 64-slice CT scanners. The chest and abdominal scans were reviewed separately and the radiologists were blinded to tumour morphology and treatment plan whilst reviewing the chest CT findings.

Based on the chest CT findings, the patients were then grouped into 4 categories—those with no lung lesions, benign lesions, indeterminate lesions and pulmonary metastases. Pulmonary metastases were defined as multiple discrete nodules, nodules of varying sizes and/or nodules randomly distributed in the lungs.[17] Benign lesions included those containing central calcifications or fat, those with tree-in-bud appearances and sub-pleural nodes.[19] Indeterminate lesions were those that could not be catagorised into either benign or metastatic lesions, particularly solitary lung nodules.

Features of the primary tumour, including tumour size and number of hepatic lesions, were studied. The maximum diameter of the tumours in the portovenous phase (either on the axial or coronal plane) were measured and placed into 1 of these 3 groups: <5 cm, 5 cm to 10 cm and >10 cm (Table 1). The number of hepatic lesions were also placed into groups of single lesion, 2 to 3 lesions and >3 lesions (Table 2). Other associated imaging features, including the presence of vascular invasion, nodal status and presence of bone metastases, were also evaluated. Univariate analysis using chi-square or Fisher's exact test (when the cell number was <5) and simple logistic regression was performed to detect any significant association of these features with pulmonary metastases. Multivariate logistic regression was also performed to control potential confounders.

Results

Within the study period, there were a total of 780 patients in our HCC registry, of which 135 patients (male = 108, female = 27) received chest CT for exclusion of pulmonary metastases prior to LRT. The patients had a mean age of 67.4 years (range, 41 to 92 years). The aetiologies for HCC were hepatitis B (n = 63, 47%), hepatitis C-related (n = 3, 2%) and others (e.g. cryptogenic/non-alcoholic steatohepatitis) (n = 69, 51%).

The mean diameter of the tumours was 8.4 cm (range, 1.5 to 18.3). They were grouped as <5 cm (n = 38, 31%), 5 cm to 10 cm (n = 34, 27%) and >10 cm (n = 52, 42%).

Table 3. Association between Pulmonary Metastases with Presence of Vascular Invasion

	No Vascular Invasion	Vascular Invasion (Hepatic/Portal Vein or Both)	Total
Benign or no lung lesions	87	20	107
Lung metastases	9	8	17
Total	96	28	124

P value from Pearson's chi-square = 0.009.

The number of intrahepatic tumours were grouped either as single lesion (n = 67, 54%), 2 to 3 lesions (n = 26, 21%) or >3 lesions (n = 31, 25%). Twenty-eight (23%) of the tumours had vascular invasion, 8 (6%) had nodal invasion, and 7 (5%) demonstrated bone metastases.

Among these 135 patients, 61 patients had abnormal chest CT findings. Seventeen patients were found to have pulmonary metastases (12.7%), 33 patients had benign lung lesions (26.7%) and 11 patients had indeterminate lesions (8.1%). Examples of chest CT findings of all separate categories are shown in Figure 1. Among the patients with indeterminate lesions, 6 were later diagnosed on biopsy or follow-up imaging to be benign lesions. The rest of the 5 patients either defaulted on follow-up (n = 2) or died before the follow-up study (n = 3). These patients were also excluded from further analysis (Fig. 2). Among the 17 patients with pulmonary metastases, locoregional therapy was precluded as a result of the findings.

Table 4. Predictors for Extrahepatic Metastasis: Multivariate Analysis

Variables	Odds Ratio (95% CI)	*P* Value
No. of liver lesions		
1	1	
2 to 3	9.66 (1.63 to 57.16)	0.012
>3	7.61 (1.26 to 45.04)	0.027
Tumour size		
Less than 5 cm	1	
5 cm to 10 cm	1.40 (0.11 to 17.8)	0.80
More than 10 cm	4.48 (0.51 to 39.58)	0.18
Presence of vascular invasion		
No vascular invasion	1	
Portal vein invasion only	2.11 (0.49 to 9.08)	0.312
Hepatic vein invasion only	2.77 (0.21 to 37.2)	0.442
Both hepatic and portal invasion	11.77 (1.08 to 128.82)	0.043

Univariate analysis showed statistically significant associations between pulmonary metastases with larger primary tumour size (Fisher's exact test, $P = 0.018$) (Table 1), increased number of intrahepatic lesions (Fisher's exact test, $P < 0.01$) (Table 2) and presence of vascular invasion (chi-square test, $P < 0.01$) (Table 3). No statistically significant association was detected between pulmonary metastases and presence of nodal involvement (Fisher's exact test, $P = 0.078$) or bone metastases (Fisher's exact test, $P = 0.245$).

On multivariate analysis (Table 4), the presence of multiple intrahepatic lesions (2 to 3 liver lesions [OR: 9.7; 95% CI,

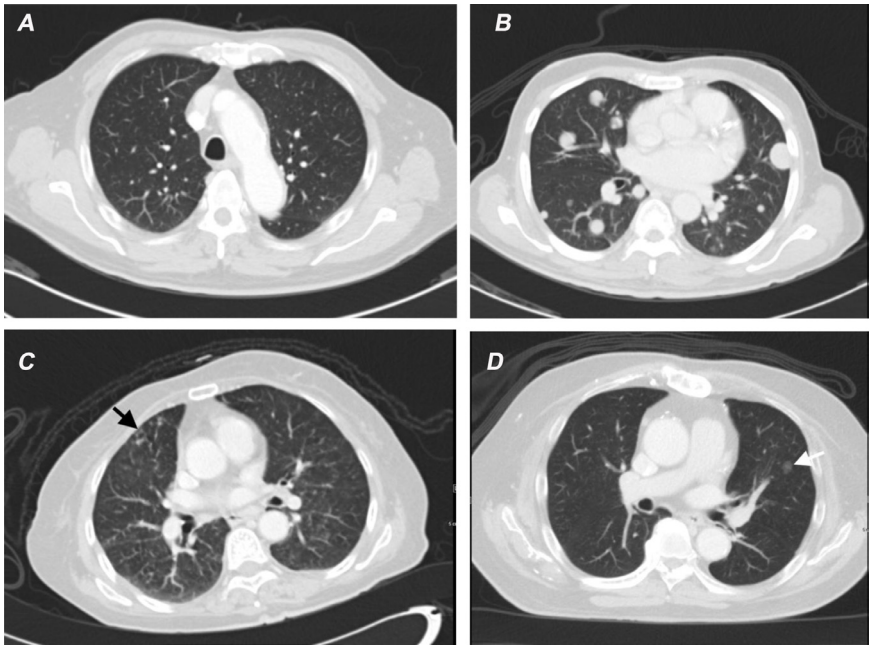

Fig 1. Examples of chest CT findings in all 4 categories. A) No lung lesion. Chest CT shows no focal abnormality. B) Pulmonary metastases. Chest CT shows multiple nodules of varying sizes scattered in both lungs. C) Benign lesion. Chest CT shows tree-in-bud nodules in the periphery of the right upper lobe (black arrow), in keeping with inflammatory change. D) Indeterminate lesion. Chest CT shows a solitary ground glass lesion in the left upper lobe (white arrow).

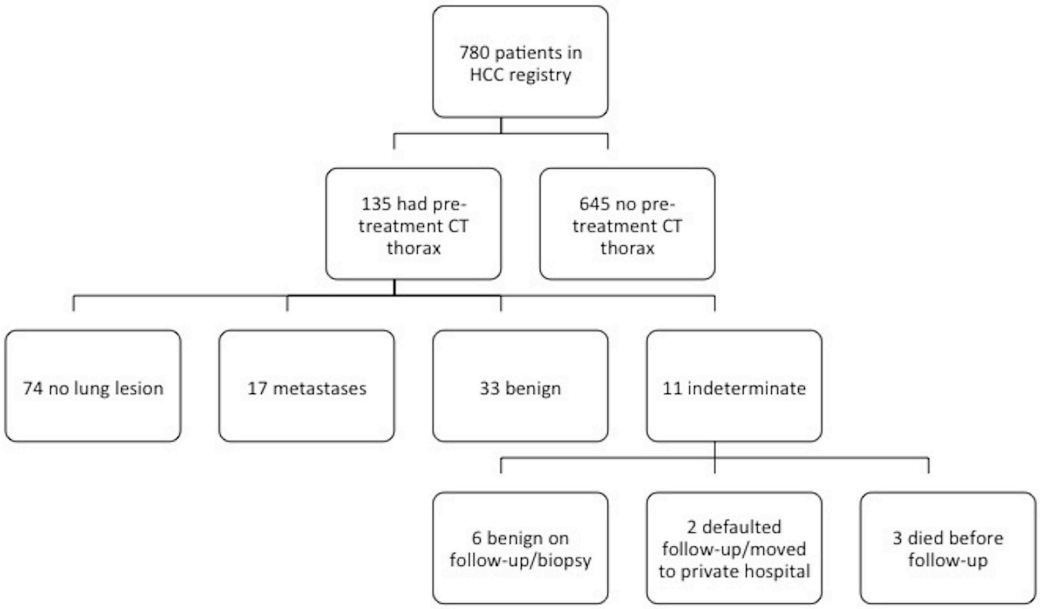

Fig. 2. Flowchart demonstrating CT thorax findings.

1.6 to 57.2; $P = 0.012$]) (more than 3 liver lesions [OR: 7.6; 95% CI, 1.3 to 45.0; $P = 0.027$]) and the presence of both hepatic and portal venous invasion (OR: 11.8; 95% CI, 1.1 to 128.8; $P = 0.043$) were the 2 independent positive predictors of pulmonary metastases with statistical significance. The size of tumour was not found to be a significant independent predictor for pulmonary metastases (5 cm to 10 cm [OR: 1.4; 95% CI, 0.1 to 17.8; $P = 0.8$]) (>10 cm [OR: 4.5; 95% CI, 0.5 to 39.6; $P = 0.2$]).

Discussion

The lung is the most common site of extrahepatic metastasis in HCC[9-11,20] and its presence excludes patients from curative locoregional therapy.[5-8] Chest CT could therefore, in theory, play an important role in pre-treatment stratification. To this end, the role of pre-treatment chest CT has not been described in commonly used staging and treatment systems such as the BCLC.[8] Review of the literature revealed limited recommendations regarding the role of chest CT in pre-treatment staging. The British Society of Gastroenterology recommends a baseline chest CT for newly diagnosed HCC patients.[21] However, this is largely based on consensus and the utility of pre-treatment chest CT remains to be systematically studied.

Issues with additional radiation burden and increased economic cost with routine staging chest CT would also require additional data to be resolved. In addition, false-positives such as indeterminate lung lesions (8% of our patients) also pose a clinical dilemma to the clinicians, resulting in increased patient anxiety and possible treatment delay from additional investigations (e.g. biopsy, positron emission tomography [PET]/CT, etc). Notably, while we identified 17 patients with lung metastasis in our study, of the 11 patients with indeterminate lung lesions, 6 who had undergone subsequent biopsy or follow-up imaging were eventually found to have benign lesions.

Furthermore, the prevalence of lung metastasis is low. The yield of lung metastases in our study population was at 12.7% which correlates with similar low figures of between 4.5% to 20% as reported in other studies that evaluated extrahepatic metastases of HCC,[10,11,20] even though these studies did not directly address the use of chest CT in the pre-treatment staging. A prior study by Jin et al of 381 patients that evaluated the value of staging chest CT with bone scan for HCC concluded that the staging scans did not contribute to significant changes to HCC BCLC staging.[17] Based on our findings, we concur that routine staging chest CT prior to LRT should not be recommended.

The decision for staging chest CT is currently largely dependent on clinician discretion and experience. In our institution, this decision is usually based on a combined tumour board decision and CT thorax is typically reserved for intermediate to advanced staged HCC. There is, however, no fixed criterion and this also presents as an inherent bias in our study group. This lack of standardisation and evidence on the usage of chest CT is part of the impetus for our study to further understand the role (if any) of staging chest CT scans and better strategise its use. Notwithstanding, routine pre-treatment chest CT is not currently practised by our

clinicians as reflected by a majority of our patients (82.7%) who have not undergone a pre-treatment chest CT.

Our study found statistically significant association between pulmonary metastases with tumour size (Table 1), number of intrahepatic lesions (Table 2) and presence of vascular invasion on univariate analysis (Table 3). This result is similar to that in a previous study conducted by Kanda et al which found that the maximum tumour diameter, number of HCC nodules and presence of vascular tumour invasion to be predictors of extrahepatic metastasis (including extrathoracic metastases).[11] On multivariate analysis, our study found the presence of multiple hepatic lesions (2 or more lesions) and the presence of both hepatic and portal venous invasion to be the 2 independent positive predictors of pulmonary metastases. This also corroborates with findings by M Natsuizaka et al that found most patients with extrahepatic metastases (including extrathoracic metastases) had multiple hepatic tumour and vessel invasion.[9] Since hematogenous dissemination to the pulmonary capillaries is the proposed mechanism of the spread of lung metastases,[10] it would explain the positive association between the presence of vascular invasion and lung metastases. Multiple liver tumours may also increase the risk of microvascular invasion and tumour seeding into the lungs. It is therefore reasonable to suggest that staging chest CT could be considered for patients with multiple hepatic lesions or vascular invasion.

Our study was limited by several factors. Most notably, it was a retrospective study with selection bias for patients who received a chest CT, which was compounded by undefined selection criteria by the referring clinicians. There were also losses to follow-up (n = 5). Our small sample size also presents a statistical challenge.

Conclusion

Based on our study results, routine staging chest CT is not necessary in all treatment-naïve HCC patients prior to LRT. Its use, however, should be considered in cases with multiple (2 or more) hepatic lesions or vascular invasion. This deserves further investigation through a prospective study with defined at-risk groups.

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Commentary

Benefits of Population Segmentation Analysis for Developing Health Policy to Promote Patient-Centred Care

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Introduction

The philosophy of patient-centred care requires a paradigm shift away from fragmented institution-centred care to integrated care models such as care teams that develop and implement a care plan tailored to meet patient needs.[1] While no 2 patients are exactly alike, it is not feasible to focus at the granular level when developing health policies that promote patient-centred care. Segmenting the population into relatively homogeneous, distinct subgroups promotes the development of care models tailored to similar groups of people rather than individuals.[2,3]

Population segmentation, with the aim of optimising healthcare services, originally evolved from market segmentation. Widely applied in the field of business, market segmentation involves tailoring product features for different consumer types.[4] Population segmentation analysis can happen at various levels—at the macro (e.g. nationwide population), meso (e.g. diabetic patients), and micro levels (e.g. individual adverse event risk stratification)[3]—with the segments themselves being derived either through expert inputs or post-hoc using statistical methods applied to empirical data.[4]

In order to prepare for an ageing population in Singapore,[1] initiatives to integrate care through population segmentation have already been started, such as those by the Agency for Integrated Care.[5] As resources are finite, targeted and high value interventions that are enabled by population segmentation analysis have become increasingly relevant. In this article, we discuss the specific benefits of population segmentation analysis for the provision of efficient patient-centred care. These include the facilitation of healthcare service planning, promoting the evaluation of health service innovations and improving care integration.

Healthcare Service Planning

Various definitions of needs exist.[6] In the healthcare context, a need is defined as the capability to benefit from healthcare.[7] Benefits can be quantified in various ways depending on the policy objective,[8] for example, cost-effectiveness, number benefiting[7] or decreased probability of transitioning into a worse health state. The goal of the healthcare system, therefore, is to match services to healthcare needs. Failure to meet the healthcare needs of patients typically leads to worse clinical outcomes and may potentially increase health service utilisation in the long-term.[7] For example, patients with atrial fibrillation on warfarin are at increased risk of either embolic stroke or severe bleeding with suboptimal anticoagulation management (i.e. international normalised ratio outside the target range).[9] Providing services beyond needs are not associated with improved outcomes (and may be associated with avoidable complications) but is surely associated with increased costs.[10] Therefore, it is important to tailor healthcare services to patient needs.[7,11]

Segmenting the population facilitates the efficient development of service packages that are based on common sets of needs associated with each segment. Understanding the needs of distinct population segments may also help ease the identification of frequently unmanaged needs by comparing services recommended to individuals in a particular segment with the typical service packages received by patients in that segment. Examples of healthcare needs assessment tools include EasyCare,[12] Interrai[13] and the Simple Segmentation Tool which is a locally developed tool.[14] Insights into the number of individuals in the various segments and current patterns of care can help policymakers plan and allocate healthcare resources at a population level.[15] In addition, policymakers will also be able to evaluate transition rates of patients between population segments and characterise risk factors for adverse transitions as potential targets for policy intervention.

Programme Evaluation

The evaluation of efforts to improve health services such as integrated care[4] is complicated by the relationship between patient characteristics and clinically relevant outcomes such

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as mortality, healthcare utilisation costs[16] and transition rates into worse health states.[17] Population segmentation analysis enables health outcome tracking for groups of patients with relatively homogeneous prognosis and similar responses to healthcare. Examples of patient segmentation schemes intended to promote programme evaluation include Kaiser Permanente's Senior Segmentation Algorithm patient groups[18] and the Bridges to Health model patient segments by Lynn et al.[2]

Care Integration

Integration of care can happen both horizontally and vertically. Horizontal integration refers to the provision of various allied health services, in addition to medical care by physicians, to address patients' manifold healthcare needs.[19] Vertical integration involves linkages across various venues of care from primary care clinics to tertiary general hospitals. Integrated care often involves the provision of a package of healthcare services, supported by benchmark tools such as guidelines and care pathways.[1] Segmentation may also help to inform policymakers on deciding which services should be included in a healthcare service package for a particular population segment. By identifying the combination of health and social service needs within different population segments, integrated packages of care can then be tailored to meet the needs of patients in their respective segments. For example, Valkronic is an integrated care programme in Spain for patients suffering from long-term conditions.[3] In this programme, patients are placed into different hospitalisation risk segments, with each receiving different service packages. Patients at the highest risk segment receive personalised education as well as tele-health services such as communication with a primary care physician via tablet computers and disease-specific biometric tele-monitoring devices. Meanwhile, patients in the lowest risk segment receive communication and education through web portals. The programme has been reported to improve clinical outcomes such as reduced utilisation of emergency care services.[3]

Furthermore, an important component of segmentation is that it logically includes social needs associated with clinically relevant outcomes. For example, loneliness is highly predictive of healthcare utilisation among the elderly,[20] particularly for those with multiple chronic conditions. Befriending services has the substantial potential to reduce healthcare utilisation for this population group and thus, should be made available in the healthcare service package delivered to this group.

Conclusion

With an ageing population, the needs for health and health-related social services in Singapore are rapidly changing. Understanding the nature of these needs through population segmentation analysis holds significant potential for helping Singapore weather the “silver tsunami”. Thus, it is recommended that healthcare institutions utilise population segmentation analysis to plan for tailored healthcare services by leveraging on pre-existing resources such as the National Electronic Health Records, as well as investing in both academic and institutional expertise to support segmentation type work.

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Assessment of Genotypic Macrolide Resistance among *Mycoplasma pneumoniae* Infections in Children in Singapore

Dear Editor,

Mycoplasma pneumoniae belongs to the class *Mollicutes* and is a small bacterium without a cell wall that is a common cause of community-acquired pneumonia in adults and children. Due to its unique physical structure, *M. pneumoniae* is resistant to cell wall-targeting agents, such as beta-lactam antibiotics. Therefore, the antibiotics of choice for the treatment of suspected *M. pneumoniae* infections, particularly for children, are the macrolides, with their main class representative being erythromycin. Alternatives for treatment include the tetracyclines and fluoroquinolones.

Reduced susceptibility or resistance of *M. pneumoniae* to macrolide antibiotics has been described; this is the consequence of point mutations in domain V (peptidyltransferase region) of the 23S rRNA gene.[1,2] The most common mutation is the substitution of adenine with guanine (A2063G) at base position 2063 (*M. pneumoniae* numbering, equivalent to base position 2058 in *Escherichia coli*).[3] This mutation has been found associated with a 10^3-fold to $>10^5$-fold elevation of the minimum inhibitory concentration (MIC) of erythromycin as compared to susceptible strains.[4] Less common mutations occur at positions 2063 (A→T, A→C), 2064 (A→G, A→C), 2067 (A→G) and 26172 (the latter not studied in this work). These mutations reduce the affinity of macrolides for the ribosome,[4,5] thereby reducing their efficacy. Macrolide resistance due to *erm* genes or enzymes that inactivate macrolides have not been detected thus far in *M. pneumoniae*.[2]

Studies conducted from 2011 onwards in Japan,[2] South Korea[2] and China[2] have demonstrated alarmingly high levels of macrolide resistance (ranging from 63% to 98%) in *M. pneumoniae* strains. On the other hand, macrolide resistance in *M. pneumoniae* from Europe,[2] North America[2] and Australia[2] has been less common (ranging from 0% to 26%). The prevalence of macrolide resistance in *M. pneumoniae* in Singapore or its neighbouring countries in South-east Asia is currently unknown. Thus, we sought to determine the prevalence of genotypic macrolide resistance in *M. pneumoniae* among clinical specimens submitted for diagnostic purposes at a paediatric hospital in Singapore. We used PCR primers published by Wolff et al[6] to amplify a region that encompasses the mutations at positions 2063, 2064 and 2067 that account for more than 99% of macrolide resistance in published works.[2]

Materials and Methods

The microbiology laboratory at KK Women's and Children's Hospital receives throat swabs and other respiratory tract specimens for a diagnostic *M. pneumoniae* polymerase chain reaction (PCR) test. This PCR assay uses a combination of 2 primers and a dual-labelled probe that targets the *M. pneumoniae* community-acquired respiratory distress syndrome (CARDS) toxin gene, as described by Winchell et al.[7] We selected consecutive nucleic acid extracts submitted between 1 January 2013 and 31 March 2014 that were positive for *M. pneumoniae* and had a threshold cycle (Ct) of less than 30 in the diagnostic PCR assay. This cutoff was chosen based on preliminary experiments (data not shown) that indicated that such samples yielded sufficient amounts of DNA for sequencing reactions. A total of 327 samples were positive for *M. pneumoniae*, and 200 samples had a Ct value of <30. Using primers designed by Wolff and coworkers[6] targeting the domain V of the 23S rRNA gene of *M. pneumoniae*, we amplified a 217 base-pair fragment (from base position 1937 to 2154) (Taq Core PCR Kit, Qiagen GmbH, Germany). We purified the DNA fragment by gel extraction (Qiaquick Gel Extraction Kit, Qiagen GmbH, Germany) and dispatched the purified fragment for DNA sequencing to identify the known point mutations associated with resistance to macrolides. Multiple sequence alignment was performed on the 200 positive samples, using the wild-type *M. pneumoniae* M129 23S rRNA gene (GenBank accession number NC_000912; Gene ID 876745) as a reference (Fig. 1).

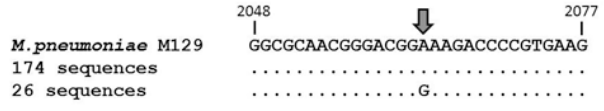

Fig. 1. Sequence alignment of domain V region of 23S rRNA genes of *M. pneumoniae* from base position 2048 to 2077. Two representative clinical samples are shown, along with their observed frequency in this study, compared to the wild-type strain M129 (GenBank accession NC_000912). Dots represent identity to the wild-type sequence. Position 2063 is indicated by an arrow.

Results

The median age of the patients from whom the samples originated was 6 years, and the age range was 0 to 15 years. There was an almost equal distribution of specimens from male and female patients. More than 90% of the patient specimens were throat swabs, with the rest made up of nasopharyngeal swabs, nasal swabs, pleural fluid and bronchioalveolar lavage. The A2063G point mutation was detected in 26 of the 200 nucleic acid extracts that were investigated. All other sequences were identical to the reference sequence of a macrolide-susceptible strain (NC_000912; Gene ID 876745). Thus, the prevalence of genotypic macrolide resistance in this cohort was 13%. None of the other mutations at base positions 2064 and 2067 that were previously associated with macrolide resistance were found.

Conclusion

To our knowledge, this is the first report on the prevalence of genotypic macrolide resistance in *M. pneumoniae* from Singapore or any other country in its direct vicinity within South-east Asia. The prevalence among Singaporean samples, collected in 2013 and 2014, was 13% based on sequencing results of the 217 base-pair region. This is within the range of 0% to 26% reported from Europe,[2] North America[2] and Australia.[2] Thus, the prevalence of genotypic macrolide resistance in Singapore is lower than might be expected from the high rates reported in East Asia. All 26 mutant sequences from Singapore contained the A2063G substitution. This is consistent with other studies that demonstrated the presence of the A2063G mutation in the vast majority (93.9%) of macrolide-resistant *M. pneumoniae*[2,3,8] compared to mutations at positions 2064 (2.8%), 2067 (0.05%) and 2617 (0.1%), which are significantly less common. There is a possibility that we may have missed mutations at base position 2617, but this would be an extremely infrequent event based on the literature.[2] The fact that all mutant strains possessed the same point mutation at base 2063 is likely a reflection of the fact that this is the most common mutation. An alternative explanation would be the clonal transmission of mutated strains, but this appears less likely, and it would require molecular typing to establish whether this was the case. In addition, our study established an estimate of the prevalence of macrolide resistance among respiratory samples submitted to our laboratory, but was not aimed at assessing pathogenicity, especially in view of the fact that it is known that *M. pneumoniae* can colonise asymptomatic children.[9]

Most infections with *M. pneumoniae* tend to take a mild-to-moderate clinical course, even if untreated or treated with ineffective antibiotics, and severe infections are uncommon.[10] Infections with macrolide-resistant *M. pneumoniae* (MRMP), when treated with macrolides, have been reported to be associated with a longer time to defervescence compared to infections with macrolide-susceptible strains.[10,11] Genotypic macrolide resistance was found associated with treatment failure in a case of severe pneumonia reported from Hong Kong.[12] The correlates for severe illness in *M. pneumoniae* infections are not fully understood, and lung injury may be related to the host cell-mediated immune response.[13] The authors of a recent review concluded that no change away from primary macrolide therapy is required in countries that have a low incidence of MRMP infections, and a replacement with fluoroquinolones or tetracyclines should be considered in regions where MRMP are common.[10] A change of antibiotics should also be considered if symptoms persist or if there is clinical deterioration, and primary treatment with other antibiotics should be considered when infections are severe, even in the early phase.[10]

One limitation of our study is that these data reflect the situation among the Singaporean paediatric population, but not necessarily among the adult population. In addition, we did not perform phenotypic tests for macrolide resistance because we did not perform cultures. However, previous studies by other researchers have shown that other mechanisms of macrolide resistance are rare.[2,14]

Susceptibility testing for *M. pneumoniae* is not routinely performed in diagnostic laboratories, but the knowledge of local macrolide resistance is useful to guide empiric therapy. Our findings indicate that the prevalence of macrolide resistance in *M. pneumoniae* strains from paediatric patients in Singapore is relatively low. That would imply that a change away from primary macrolide treatment for *M. pneumoniae* infections is not indicated at this point in time. There is a possibility that MRMP may spread rapidly[15] and thus, periodic surveillance for resistance to macrolides appears necessary to detect emerging resistance.

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Osteonecrosis in Adolescents and Young Adults with Acute Lymphoblastic Leukaemia on Hong Kong-Singapore Acute Lymphocytic Leukaemia 97 Protocol

Dear Editor,

Osteonecrosis (ON), a debilitating disease frequently involving multiple joints, has been recognised in recent years as a severe complication of acute lymphocytic leukaemia (ALL) therapy in adolescents and young adults. It hence presents a challenging obstacle in modern chemotherapy.[1]

There are several well-known risk factors for the development of ON, including the use of dexamethasone, age over 10 years and the female gender.[2,3] Another possible factor is the presence of certain genetic polymorphisms, such as in the *ACP1* gene (a regulator of lipid levels and osteoblast differentiation)[4] or *BMP7* gene (the BMP7 protein product is known to be toxic to bone vasculature).[5]

Other studies have also shown that high body mass index, low albumin levels and elevated cholesterol can be linked to ON.[4] The precise mechanism by which ON develops still remains unknown but administration of corticosteroids has been shown to cause ischaemia and induce excessive apoptosis of osteoblasts and osteocytes.[6]

In studies conducted in the United States and Europe, the overall incidence of ON in childhood ALL patients was highly variable, ranging from 1% to 9%.[1-3] A study conducted by the Japanese Childhood Cancer and Leukemia Study Group found an overall ON incidence of 1.5%,[7] comparable to previous studies. This study additionally found a significant correlation between age and ON incidence, with incidence rates of 0.42% for age less than 10 years versus 15.6% for age 10 years and above ($P < 0.0001$). This suggests that adolescents and young adults are at much greater risk of ON as compared to younger age groups.

One suggestion is that alternate-week steroid scheduling, instead of continuous, is a feasible way to prevent treatment-related ON.[8] However, empirical therapy for childhood ALL patients with ON is still lacking, due to a paucity of good quality studies. Greater understanding of individual risk factors and the underlying physiology in adolescents and young adults is still needed to improve prediction and management of ON in this population.

In this study, a retrospective analysis of adolescents and young adults aged 13 to 21 years with ALL, diagnosed and treated at a large tertiary hospital's haematology department, was conducted. These patients were treated with the Hong Kong-Singapore (HK-SG) 97 protocol, a Berlin-Frankfurt-Munster (BFM)-based, paediatric-inspired protocol. We aimed to evaluate the incidence and outcomes of ON within this population while outlining some recommendations to mitigate this problem.

Materials and Methods

From January 2009 to December 2014, all adolescents and young adults aged 13 to 21 years and newly diagnosed with ALL were treated with the HK-SG 97 regimen (Table 1). This diagnosis was made according to the World Health Organisation 2008 criteria, involving assessment of bone marrow morphology, karyotyping and molecular studies for *BCR/ABL* translocation. A retrospective review of the data was conducted from the Leukemia Registry and was approved by the institutional review board.

The HK-SG 97 protocol was previously used by the Hong Kong Paediatric Haematology and Oncology Study Group in a study of paediatric patients.[9] Patients are classified as high-risk if they have one of the following characteristics: 1) t(9;22) or *BCR-ABL* fusion; 2) t(4;11) or *MLL-AF4* fusion; 3) resistance to prednisolone, defined as absolute peripheral blast count >1 x 10^9/L on day 8 of pretreatment phase with prednisolone; and 4) ≥5% blasts in bone marrow on day 33 of induction phase 1A. All other patients are classified as intermediate risk.

Results

A total of 16 patients, 9 males (56%) and 7 females (44%), met the diagnostic criteria for ALL. Median age at diagnosis was 19 years. In our patient cohort, 62.5% of the patients were categorised as intermediate risk and the remaining 37.5% as high risk.

Of the 16 patients, 5 (31.3%) developed ON. Four were from the intermediate risk group. One of the 5 patients had ON diagnosed during salvage therapy and the other 4 were diagnosed during maintenance therapy. Of these 5 patients, 4 were male and 1 was female.

Bilateral ON of the hip, involving the femoral heads, was found in 4 patients, 3 of whom needed total hip replacement, while the other received no intervention as she succumbed

Table 1. Hong Kong-Singapore (HK-SG) 97 Protocol

Intermediate Risk	Day of Chemotherapy	High Risk	Day of Chemotherapy
Pretreatment		Pretreatment	
Prednisolone 20 mg/m^2 (PO)	1	Prednisolone 20 mg/m^2 (PO)	1
Prednisolone 40 mg/m^2 (PO)	2	Prednisolone 40 mg/m^2 (PO)	2
Prednisolone 60 mg/m^2 (PO)	3 – 7	Prednisolone 60 mg/m^2 (PO)	3 – 8
MTX 12 mg (IT)	Once	MTX 12 mg (IT)	Once
Induction 1A		Induction 1A	
Danorubicin 30 mg/m^2 (IV)	8, 15, 22, 29	Danorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29	Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
Prednisolone 60 mg/m^2 (PO) then taper	8 – 28	Prednisolone 60 mg/m^2 (PO) then taper	8 – 28
L-asparaginase 5000 IU/m^2	12, 15, 18, 21, 24, 27, 30.33	L-asparaginase 5000 IU/m^2	12, 15, 18, 21, 24, 27, 30.33
MTX + Cytarabine + Hydrocort (IT)	15, 33	MTX + Cytarabine + Hydrocort (IT)	15, 33
MTX + Cytarabine + Hydrocort (IT)*	8, 22	MTX + Cytarabine + Hydrocort (IT)*	8, 22
Induction 1B		Induction 1B	
Cyclophosphamide 1000 mg/m^2 (IV)	36, 64	Cyclophosphamide 1000 mg/m^2 (IV)	36, 64
Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48, 52 – 55, 59 – 62	Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48, 52 – 55, 59 – 62
MTX + Cytarabine + Hydrocort (IT)	45, 59	MTX + Cytarabine + Hydrocort (IT)	45, 59
6-MP 60 mg/m^2 (PO)	36 – 63	6-MP 60 mg/m^2 (PO)	36 – 63
Consolidation Protocol M		Block 1	
Methotrexate 5000 mg/m^2 (IV)	8, 22, 36, 50	Vincristine 1.5 mg/m^2 (IV)	1, 6
MTX + Cytarabine + Hydrocort (IT)	8, 22, 36, 50	Methotrexate 5000 mg/m^2 (IV)	1
6-MP 25 mg/m^2 (PO)	1 – 56	Cytarabine 2000 mg/m^2 (IV)	5
		L-asparaginase 25000 IU/m^2 (IV)	6
		MTX + Cytarabine + Hydrocort (IT)	1
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
		6-MP 100 mg/m^2 (PO)	1 – 5
		Block 2	
		Vincristine 1.5 mg/m^2 (IV)	1, 6
		Methotrexate 5000 mg/m^2 (IV)	1
		Cyclophosphamide 150 mg/m^2 (IV)	1 – 5
		L-asparaginase 25000 IU/m^2 (IV)	5
		Daunorubicin 50 mg/m^2 (IV)	5
		MTX + Cytarabine + Hydrocort (IT)	1
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
		6-MP 100 mg/m^2 (PO)	1 – 5
		Block 3	
		Cytarabine 2000 mg/m^2 Q12H (IV)	1 – 2
		Etoposide 150 mg/m^2 (IV)	3 – 5
		L-asparaginase 25000 IU/m^2	5
		MTX + Cytarabine + Hydrocort (IT)	5
		Dexamethasone 20 mg/m^2 (PO)	1 – 5
Reinduction 2A		Reinduction 2A	
Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29	Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29	Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
L-asparaginase 10000 IU/m^2 (SC)	8, 11, 15, 18	L-asparaginase 10000 IU/m^2 (SC)	8
Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21	Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21
MTX + Cytarabine + Hydrocort (IT)*	1, 8		

6-MP: 6-Mercaptopurine; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate; PO: Per oral; RT: Radiotherapy; SC: Subcutaneous
*Patients with central nervous system involvement received these additional treatments.

Table 1. Hong Kong-Singapore (HK-SG) 97 Protocol (Cont'd)

Intermediate Risk	Day of Chemotherapy	High Risk	Day of Chemotherapy
Reinduction 2B		Reinduction 2B	
Cyclophosphamide 1000 mg/m^2 (IV)	36	Cyclophosphamide 1000 mg/m^2 (IV)	36
Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48	Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48
MTX + Cytarabine + Hydrocort (IT)	38, 45	MTX + Cytarabine + Hydrocort (IT)	38, 45
Cranial irradiation	36 – 50	6-MP 60 mg/m^2 (PO)	36 – 49
Maintenance (10 weekly for 24 months)		Interim maintenance	
Vincristine 1.5 mg/m^2 (IV)	57, 64	MTX + Cytarabine + Hydrocort (IT)	7, 14
Methotrexate 20 mg/m^2 (PO)	57	6-MP 50 mg/m^2 (PO)	1 – 28
MTX + Cytarabine + Hydrocort (IT)	1 – 70	Methotrexate 20 mg/m^2 (PO)	7, 14, 21, 28
6-MP 50 mg/m^2 (PO)	57 – 63	Cranial RT	8 – 22
Dexamethasone 6 mg/m^2 (PO)			
		Reinduction 3A	
		Doxorubicin 30 mg/m^2 (IV)	8, 15, 22, 29
		Vincristine 1.5 mg/m^2 (IV)	8, 15, 22, 29
		L-asparaginase 10000 IU/m^2 (SC)	8
		Dexamethasone 10 mg/m^2 (PO) then taper	1 – 21
		Reinduction 3B	
		Cyclophosphamide 1000 mg/m^2 (IV)	36
		Cytarabine 75 mg/m^2 (SC or IV)	38 – 41, 45 – 48
		MTX + Cytarabine + Hydrocort (IT)	38, 45
		6-MP 60 mg/m^2 (PO)	36 – 49
		Maintenance (10 weekly for 24 months)	
		Vincristine 1.5 mg/m^2 (IV)	57, 64
		6-MP 50 mg/m^2 (PO)	1 – 70
		Methotrexate 20 mg/m^2 (PO)	7, 14, 21, 28, 35, 42, 49, 56, 63, 70
		Dexamethasone 6 mg/m^2 (PO)	57 – 63

6-MP: 6-Mercaptopurine; IT: Intrathecal; IV: Intravenous; MTX: Methotrexate; PO: Per oral; RT: Radiotherapy; SC: Subcutaneous

*Patients with central nervous system involvement received these additional treatments.

to disease. One of these patients additionally had ON of the left shoulder, while 2 others also had multiple ON foci of the pelvic bones and sacrum. The fifth patient had ON of the right knee involving the femoral condyle, which required knee core decompression.

In 4 of the 5 patients, excluding the one who succumbed to disease, the first complaint of pain in the joint was reported during maintenance therapy. Subsequent magnetic resonance imaging (MRI) then revealed ON of the hip or knee. All total hip replacements, as well as the knee core decompression, were carried out after the completion of maintenance chemotherapy. All operations were performed successfully and without further complications. These 4 patients were still alive as of last follow-up, with a median survival of 70 months.

The last patient's ON of the hip was diagnosed incidentally on computerised tomography (CT) scans of the abdomen and pelvis which were done as part of investigations for sepsis.

Table 2 summarises these patients' osteonecrosis diagnosis and outcomes.

Discussion

Although a number of studies found the female gender to be a significant risk factor in developing ON,[1,2] this was not so for our cohort, where 80% of our patients with ON were male, from a cohort of 56% males and 44% females. Additionally, other studies performed in the United Kingdom and United States did not find such a correlation between ON incidence and the female gender.[10] As such, the impact of gender on ON pathogenesis remains controversial.

Dexamethasone has been increasingly used in ALL

Table 2. Patient Characteristics, ON Diagnosis and Outcomes

Patient No.	Gender	ALL Risk Stratification	Phase of Chemotherapy in Which ON Was Diagnosed	Site of Osteonecrosis	Surgical Procedures Performed	Survival (Months)
1	M	IR	Maintenance	Right knee	Right knee core decompression	32
2	M	IR	Maintenance	Bilateral hips, multiple foci in pelvic bones and sacrum	Bilateral THR	72
3	M	HR	Maintenance	Bilateral hips, left shoulder	Right THR	86
4	M	IR	Maintenance	Bilateral hips, multiple foci in pelvic bones and sacrum	Bilateral hip core decompression, left THR	67
5	F	IR	Salvage	Right hip	None	18

ALL: Acute lymphocytic leukaemia; F: Female; HR: High risk IR: Intermediate risk; M: Male; ON: Osteonecrosis; THR: Total hip replacement

protocols as it is more cytolytic compared to steroids.[11] However, dexamethasone is also more toxic to bone tissue,[12] resulting in a higher ON incidence. The Japanese Children's Cancer and Leukemia Study Group[7] found that ON was most prevalent in patients receiving only dexamethasone, suggesting that dexamethasone administration at any dose and in any treatment phase increases ON incidence.

A study done at St Jude Children's Research Hospital of 89 adolescents and young adults aged 15 to 18 years reported an ON incidence of 32.9%,[13] comparable to the 31.3% incidence within our study population. Total steroid doses in the St Jude study were lower than those used in our protocol. However, our incidence rate was also markedly higher than other reported incidences.[2,3] Comparing with the BFM 95 regime, which the HK-SG 97 was adapted from, our ON incidence is higher than the reported incidence of 11.1% among patients aged 14 to 18 treated with BFM 95.[1] This is despite the HK-SG 97 protocol having a similar total steroid dose for intermediate risk patients, and a lower total steroid dose for high risk patients, as compared to the BFM 95. This could possibly be due to the different racial heritage between the patients in the various studies, resulting in different genetic predispositions. It is also noted that our small sample size may give rise to a larger margin of random error, thus it would have been ideal to use a larger study cohort.

A few methods have been employed to reduce the risk of ON in adolescents and young adults with ALL. One of them is the practice of pre-emptive MRI of hips and knees soon after reinduction, in the hope that early detection would allow for therapeutic intervention such as steroid dose reduction.[13] This would also help in identifying asymptomatic ON. Additionally, another study found that alternate-week, instead of continuous administration of dexamethasone during delayed intensification therapy, lowered the incidence of ON.[14]

Conclusion

In view of our high ON incidence, we should strongly consider the strategies of early MRI screening and alternate-week dexamethasone therapy. Additionally, screening patients for relevant genetic polymorphisms in genes such as *ACP1* and *BMP7* could help identify those predisposed towards ON.

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Non ST-Elevation Myocardial Infarction in a Patient with Supravalvular Aortic Stenosis. Role of Multi-Modality Imaging

Dear Editor,

Supravalvular aortic stenosis (SVAS) is a congenital narrowing of the ascending aorta above the level of sinus of Valsalva. It is most often commonly associated with William's syndrome although it can arise without syndromic associations as well.[1,2] Left main coronary artery (LMCA) occlusion or stenosis has been seen to be associated with the condition, and can be a cause of sudden cardiac death in such patients.[3,4,5,6]

Case Report

A 29-year-old female was admitted to our centre with chest pain and shortness of breath while performing strenuous aerobic exercises. She had a history of non-syndromic congenital supravalvar aortic stenosis (SVAS) and was non-compliant to follow-ups. She was previously offered surgery but had refused surgical intervention.

Upon presentation, her electrocardiogram was consistent with that of a left main coronary artery (LMCA) occlusion and showed for global deep ST depressions with reciprocal ST elevations in aVR. Her symptoms abated promptly with rest in the Emergency Department, with resolution of accompanying electrocardiographic changes (Fig. 1). A bedside echocardiogram showed intact wall movements. Serially trended troponin I measurements peaked at 31.6 ug/L (normal <0.039).

She was admitted to the Coronary Care Unit and managed conservatively with close monitoring of haemodynamics. Cardiac computed tomography (Fig. 2) showed normal coronary vessels with an elongated left coronary cusp extending to the sinotubular junction, in close relation to the left main coronary ostium, as well as narrowing of the sinotubular junction in keeping with SVAS. On cardiac magnetic resonance imaging (Fig. 3), there was no late gadolinum enhancement in keeping with a myocardial infarction, or evidence of myocardial oedema. The sinotubular junction was also noted to be narrowed at 13 mm, whereas the annulus was 18 mm, sinus of Valsalva was 22 mm and the ascending aorta was 16 mm in diameter. The peak gradient across the supra-aortic and aortic valve segments was 63 mmHg, consistent with severe stenosis.

The patient recovered well with conservative management and was discharged with advice against excessive exercise. She was given an early appointment to consult with a view to early surgical intervention of SVAS.

Discussion

SVAS has been well described in the literature, and has associations with LMCA occlusion.[3,4,5,6] There have also been reported cases of sudden cardiac death from occlusion of the right coronary ostium.[7] It is most classically associated with William's Syndrome although it can exist independently of syndromic conditions as well.[1,2] A case series of 9 patients described 3 patterns of LMCA occlusion including ostial narrowing (type I), cusp-ridge fusion (type 2), as well as fusiform narrowing of the LMCA (type 3), and suggested differing surgical approaches for each pattern.[8]

Presentations of LMCA occlusion in association with

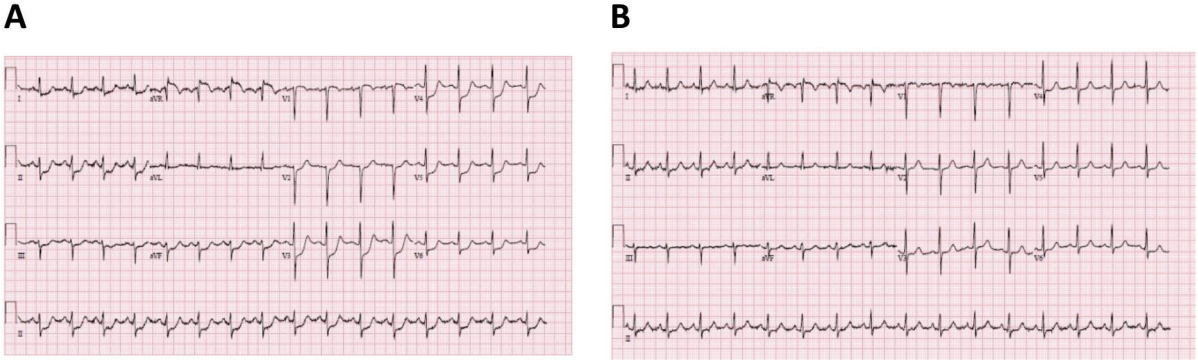

Fig. 1. Electrocardiograms upon presentation and after rest. A) Electrocardiogram shows global ST depressions with a reciprocal ST elevation of lead aVR. B) Electrocardiogram shows for resolution of ST changes with rest.

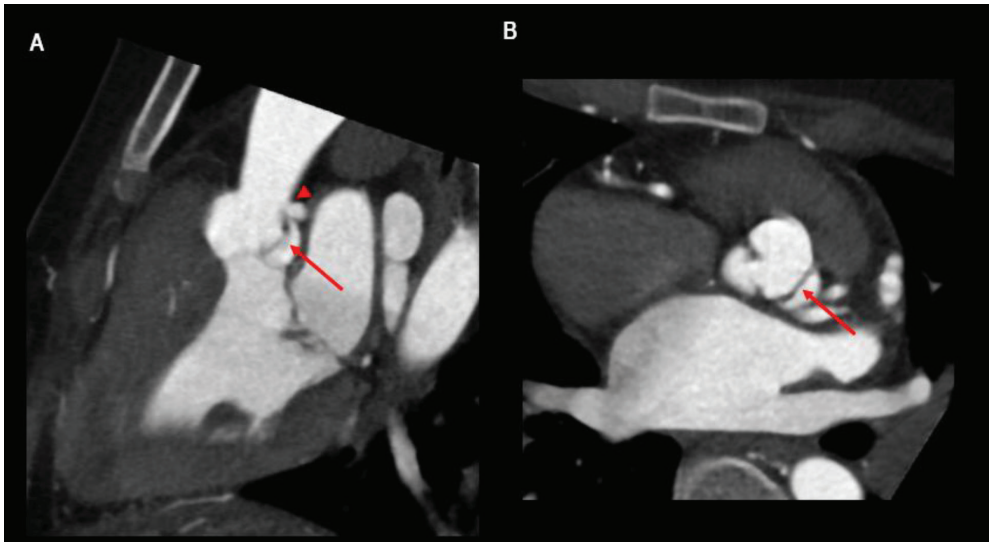

Fig. 2. Cardiac computed tomography of SVAS and origin of LMCA. Multiplanar reformats from the CT coronary angiogram study in A) left ventricular outflow tract view and B) enface view of the aortic valve at the level of the sinuses of Valsalva. This shows the elongated left coronary cusp (arrow). The tip of the left coronary cusp is seen in close relation to the ostium of the left main coronary artery (arrowhead).

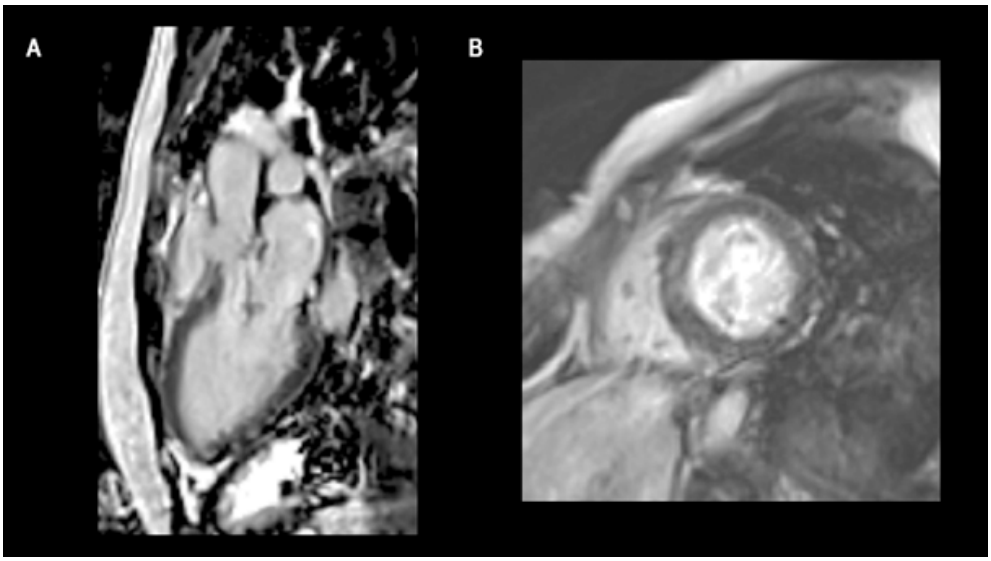

Fig. 3. Late gadolinum enhanced magnetic resonance images of the heart. Post-contrast high resolution inversion recovery magnetic images of A) 3-chamber and B) basal short axis views do not show any late gadolinium enhancement to suggest myocardial infarction, or any regional wall motion abnormalities. The sinotubular junction was also noted to be narrowed at 13 mm, whereas the annulus was 18 mm and the sinus of Valsalva was 22 mm. The peak gradient across the supra-aortic and aortic valve segments was 63 mmHg.

SVAS can be as a myocardial infarction or sudden cardiac death in a paediatric population.[3,4,5,7] Treatment tends to favour a surgical approach, combining an aortic root reconstruction for SVAS as well as either surgical repair of the left main coronary ostium or emplacement of a bypass graft.[8] In this specific case of LM coronary occlusion from cusp-ridge fusion (type 2) and SVAS, the recommended approach was excision of the valve leaflet from the aortic wall with preservation of all possible leaflet tissue, followed by an aortotomy and single patch aortoplasty with native pericardium.[8]

In the above patient, we believe that the strenuous exercises undertaken had resulted in a dynamic obstruction of the left main coronary ostium due to her unique anatomy with an ensuing presentation of chest pain with features suggestive of LMCA occlusion. Coronary artery stenosis or obstruction should hence be considered in all patients with SVAS.

The authors suggest that a non-invasive approach with close monitoring and early cardiac imaging as the above could be a viable and safe alternative to invasive coronary angiography in patients with such a presentation.

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