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Full Length Research Paper

How accurate is triaxial RT3™ (RT3) accelerometer for estimating energy expenditure?

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The participants are instructed to remove the RT3 only for sleeping, bathing and swimming activities but some studies have shown the participants remove the accelerometer for longer times. The activities performed while the accelerometer is not being worn and, or energy that was not recorded during this time has never been estimated. This study aimed to assess compliance in using the accelerometer and quantify the energy expenditure (EE) not recorded by the accelerometer during the time it was not worn in free-living young males in a consecutive 4-day period. Eleven male participants 19 to 23 years of age, 54.7 to 85.5 kg with body mass index of 19.1 to 27.6 kg.m⁻² completed the study. Resting metabolic rate was measured by indirect calorimetry. Daily EE estimation was on average 23.6% higher using the Bouchard Physical Activity Records than the RT3. Accelerometers were worn for 67 to 98% of waking hours but up to 30% of the EE was not recorded due to the device not being worn by participants mainly during intense physical activity. Recording the physical activity when the accelerometer is not being worn would provide a more precise estimative of the EE.

Key words: Energy expenditure, accelerometer, physical activity records, young men.

INTRODUCTION

Habitual physical activity (PA) has been shown to impact significantly on chronic diseases. In order to determine the optimal dose of PA to favourably modify disease risk, the volume of daily PA and energy expenditure (EE) needs to be assessed.

Objective measurement methods such as accelerometers have advantages of not relying on participant's memory. Accelerometers are frequently used to assess EE, pattern

of physical activity and intensity of the activities performed. The RT3™ triaxial accelerometer is a small, lightweight, battery-powered instrument. The sensor is an accelerometer sensitive along three orthogonal axes. The acceleration is measured periodically and stored in memory. The EE estimated from RT3 has been found to be positively correlated with that estimated from Double Labelled Water (DLW) ($r = 0.67$, $p < 0.05$, respectively) and the 95% confidence interval of the mean difference between methods is relatively small (-385 to 145 kcal/day, respectively) (Jacobi et al., 2007) showing small dispersion around the mean. The device is usually clipped to the participant's waist and the participants are instructed to remove the RT3 only for sleeping, bathing and swimming activities. However, some studies have shown the participants remove the accelerometer for longer times. Compliance wearing the accelerometer has never been systematically assessed neither have

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Abbreviations: EE, Energy expenditure; RT3, triaxial RT3™; PA, physical activity; B-PAR, Bouchard Physical Activity Record; BMI, Body mass index; RMR, resting metabolic rate; MET, metabolic equivalent; VM, vector magnitude.

the activities performed while the accelerometer is not being worn and, or the amount of energy that was not recorded during this time. Double Water Labelling (DLW) is the gold standard to assess the EE. However it does not provide any indication of the pattern of activities performed.

The Bouchard Physical Activity Record (B-PAR) (Bouchard et al., 1983) is one of the most commonly used diaries and involves the recording of PA intensity according to type of PA each 15-min throughout the day. Each score is expressed in metabolic equivalent (MET) or as kcal/kg.15 min. The MET is used as an index of the intensity of PA (Schutz et al., 2001), ranging from 1 to 18 (light to vigorous) to represent specific PA which enables comparisons between adults assuming no physical disability or other conditions that would significantly alter their mechanical or metabolic efficiency. The MET provides a convenient option to express the energy needs of a wide range of people in a standardized form (Pannemans et al., 1995).

The aim of this study was to assess compliance in using the accelerometer and quantify the energy expenditure not recorded by the accelerometer during the time it was not worn in free-living young males in a consecutive 4-day period. The hypothesis is that young males will have high compliance in using accelerometer over a period of four days and that similar daily EE will be estimated by B-PAR and RT3 accelerometer during this period.

MATERIALS AND METHODS

Participants

Eleven male Physical Education and Exercise and Sport Science students (19 to 23 years of age) were recruited. Each participant read and signed an approved written consent form in accordance with the Queensland University of Technology Human Research Ethics Committee guidelines.

Anthropometric and physiological measurements

Methods have been previously described in details (Liberato et al., 2008). In brief, anthropometric measures including body weight, height, body composition, and waist and hip circumferences were undertaken. Body mass index (BMI) was calculated as weight (kg) divided by height² (m²). Resting metabolic rate (RMR) was measured by continuous open-circuit indirect calorimetry using a Deltatrac II metabolic cart (Datex-Ohmeda Corp., Helsinki, Finland).

Physical activity measurements

Physical activity was assessed by B-PAR using nine categories of PA for each 15-min period throughout the day during a consecutive 4-day period (two week days, Saturday and Sunday) while wearing the RT3 accelerometer. These categories were explained and illustrated in detail to each participant before they started to record and the participants were allowed to clarify any doubts arising while filling the records and to change the scores if appropriate. The MET

value for each category of PA was established for its corresponding list of activities (Bouchard et al., 1983). The respective scores and specific MET values were summed for all 15-min intervals across a 24-h period and used to calculate daily EE. The EE was calculated by multiplying the MET by RMR.

The RT3™ triaxial accelerometer (Stayhealthy, Inc., Monrovia, CA) is a small (71 × 56 × 28 mm), light weight (65.2 g), battery-powered instrument. The sensor is an accelerometer sensitive along three orthogonal axes (x, y and z), which represent vertical, anteroposterior, and mediolateral motion, respectively. The accelerometers used in the RT3 have a dynamic range of 0.05 to 2.00 g, are sensitive in the range 2 to 10 Hz, and are calibrated at 5.3 Hz (Powell et al., 2003). The acceleration is measured periodically, culminating in the vector magnitude of movement (calculated as $VM = (x^2 + y^2 + z^2)^{0.5}$) and stored in memory. The EE (kcal.min⁻¹) and VM (counts.min⁻¹) outputs from the accelerometer were used in the current study. The outputs were downloaded to a PC, using specific software. The algorithm used by the accelerometer to generate its outputs is unavailable to the researchers. Prior to the commencement of recording, participants' details including age, height, weight and gender were loaded and the RT3 set to record data each minute. The device was clipped to the participant's waist and the participants were instructed to remove the RT3 only for sleeping, bathing and swimming activities. The participants were asked to record the times when the RT3 was removed.

Data analysis

Data from the accelerometer recorded each minute was summed for 15-min periods and compared to data from B-PAR which are recorded in periods of 15-min. For time periods when the participant was awake but not wearing the accelerometer, the RT3 data were considered missing and replaced by mean RT3 data corresponding to each B-PAR score when the participant was wearing the RT3.

For each participant, 15-min periods were classified into three PA levels, according to the Center for Disease Control and Prevention and the American College of Sports Medicine Position Statement (Pate et al., 1995): a) light (EE < 3 METs), moderate (3 METs ≤ EE < 6 METs) and vigorous (EE ≥ 6 METs). For the RT3, VM values corresponding to 3 and 6 METs are 984 and 2340.8 counts, respectively (Rowlands et al., 2004). The B-PAR scores 1 to 4, 5 to 7 and 8 to 9 correspond to light, moderate and vigorous PA, respectively (Bouchard et al., 1983; Dionne et al., 2000).

Statistical analysis

Univariate analysis included means and standard deviations. The agreement between B-PAR and RT3 in relation to daily EE and time engaged in PA was evaluated using scatter plots.

RESULTS

The participants were in average 21.2 ± 1.3 years old, had height of 175 ± 4.8 cm, weight of 72 ± 10.4 kg and BMI of 23.45 ± 2.68 kg/m². Daily EE estimation was on average 23.6% higher using B-PAR than the RT3 and the agreement between both methods ranged from 5 to 48%. Over a 4-day period, the accelerometer was not worn for on average 2.6 h per day during waking time, corresponding to a range of 9 to 918 kcal/day (0 to 30%) not recorded by RT3 according to participants (Table 1).

The RT3 accelerometer was not worn during 63.3% of

Table 1. Body Weight (BW), resting metabolic rate (RMR), daily energy expenditure (EE) and daily time sleeping and wearing RT3 accelerometer over 4 days in 11 young male participants.

Participant	BW (kg)	RMR (kcal.d ⁻¹)	EE (kcal)		Time (h)	
			B-PAR ¹	RT3 ²	Sleeping ³	Wearing RT3 (%) ⁴
1	76.3	1886	3436	2792	9.5	14.3 (98) ⁴
2	73.4	1843	3449	3289	6.9	13.3 (78)
3	74	1829	3676	3127	7.9	13.9 (86)
4 ⁵	61.7	1670	3368	2443	7.7	13.6 (83)
5	55.8	1814	3082	2460	8.4	12.1 (77)
6	54.7	1714	3642	2829	8.0	14.2 (89)
7	78.5	2074	4040	3389	7.4	15.9 (96)
8 ⁵	83.7	2232	4718	3583	8.0	12.4 (78)
9 ⁶	85.5	1800	3707	3417	7.8	10.9 (67)
10 ⁵	72.2	1901	4013	3157	8.2	14.0 (88)
11	76.5	1771	3291	2706	8.1	12.8 (80)
Mean	72.0	1867	3675	2868	8.0	13.4 (84)

¹B-PAR, Bouchard Physical Activity Record. ²Estimated from RT3 Accelerometer (when RT3 was not worn, EE was estimated from mean RT3 data corresponding to each B-PAR score for each participant when RT3 was worn). ³Estimated from B-PAR. ⁴Percentage of time wearing RT3 in relation to the waking hours. ⁵Data from 3 days. ⁶Data from 2 days.

Table 2. Time¹ (min.d⁻¹, average over 4 days) spent in light, moderate, and vigorous intensity physical activity estimated by Bouchard physical activity record (B-PAR) and RT3 accelerometer in 11 young male participants.

Physical activity	B-PAR	RT3	
		Recorded	Missed ²
Light (< 3 METs ³)	1281.5 ± 17.6	1204.7 ± 30.7	130.8 ± 22.8 (4 – 229) ⁴
Moderate (3 ≤ METs < 6)	110.1 ± 20.9	67.0 ± 11.3	7.8 ± 3.0 (0 – 30)
Vigorous (≥ 6 METs)	48.4 ± 8.7	10.9 ± 4.9	18.8 ± 10.4 (0 – 113)
Total	1440	1282.6	157.4

¹Mean ± SE. ² Participants were awake and not wearing the RT3 (Time estimated from B-PAR). ³Metabolic equivalent = EE / RMR. ⁴Minimum - maximum.

time completing vigorous PA (Table 2). All 11 participants estimated longer time engaged in moderate and vigorous PA by B-PAR compared to the time recorded by the RT3. Participants correctly chose B-PAR scores 1 to 4 and 9 for their PA engagement. The B-PAR scores 1 to 4 corresponding to light PA below 3 METs were below the RT3 VM value of 984 counts cut-off. Similarly, the B-PAR scores 9 corresponding to vigorous PA (above 6 METs) were above the RT3 VM value of 2340.8 counts cut-off. However, scores 5-8 did not have good correspondence with the RT3 VM outputs (Figure 1A). Scores 5 to 7 should be between 984 and 2340.8 counts cut-off but they were below 984 counts. Score 8 should be above 2340.8 counts and it was between 984 and 2340.8 counts. For each one of the nine B-PAR scores recorded by participants, the RT3 recorded a large range of VM values (Figure 1B). The agreement between B-PAR scores and RT3 VM outputs was not related to the participants' PA behaviour as there was high variability in the agreement regardless the activity level (data not shown).

DISCUSSION

At the group level, daily EE estimation was 23.6% lower using the RT3 accelerometer than the B-PAR. Lower EE (17.1%) estimated using RT3 accelerometer than that estimated using Double Labelled Water was also observed in a study including 13 overweight adults (Jacobi et al., 2007) and lower estimates of EE by Tritrac accelerometer compared to that estimated by B-PAR was found for 97% of the participants of another study (Wickel et al., 2006).

At the individual level, the difference between B-PAR and RT3 was variable, suggesting that the accuracy of B-PAR for estimating daily EE at the individual level depends on the participant's commitment. A similar finding was observed in a study with overweight women comparing EE estimated by B-PAR with that assessed by Double Labelled Water (Fogelholm et al., 1998). The difference between daily EE estimation by B-PAR and by Double Labelled Water ranged from approximately -8800

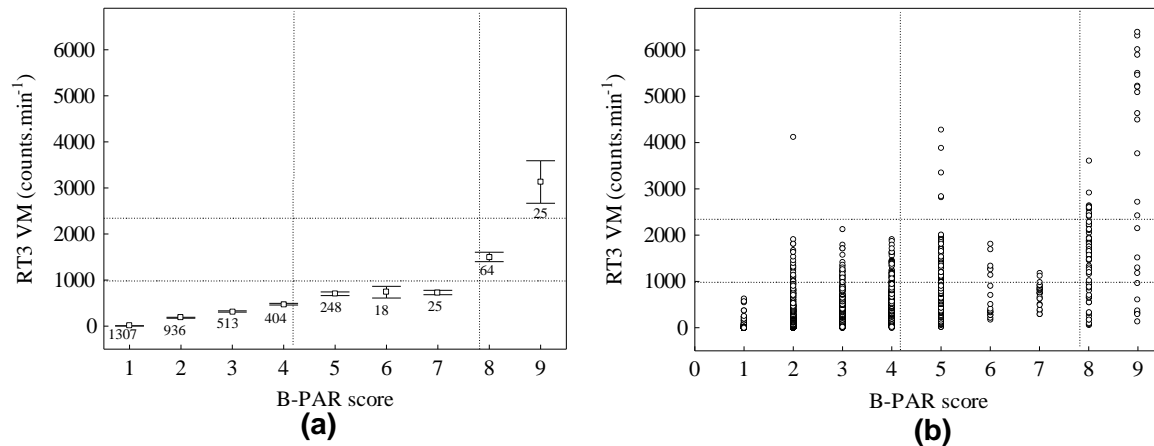


Figure 1. Vector magnitude (VM) from RT3 accelerometer in relation to B-PAR scores. a. Mean \pm standard error. (Below each mean is the number of 15-min period, recorded by 11 participants over 4 days). b. Amplitude of VM values of each score recorded. The dash lines, which represent 3 and 6 METs, are the threshold of light, moderate and vigorous PA level, being the horizontal in relation to VM according to Rowlands et al. (2004) and the vertical in relation to B-PAR.

to 15,000 kcal. Even though the participants were instructed to wear the accelerometer during all time except for sleeping, bathing and swimming activities, the RT3 was worn 84% of the waking hours (13.4 h/day). Similar periods wearing the accelerometer have been found in other studies. Leenders et al. (2001) and Cradock et al. (2004) reported that participants wore accelerometers 13.5 h/day (75 to 85% of waking time) and 12.5 h/day, respectively. A minimum of 9 to 10 h/day wearing the accelerometer has been required in some studies (Schmidt et al., 2003; Cradock et al., 2004).

Up to 918 kcal/day was missed by the RT3 because the participants were not wearing the accelerometer. This value is higher than the range of 100 to 150 kcal.day⁻¹ for missed recorded energy suggested by Leenders et al. (2001).

Most of the time accelerometer was not worn by participants of the current study was found to be while performing vigorous PA. Up to 113 min/day spent in vigorous PA was missed by the RT3. Some participants in the current study reported removing the accelerometer during moderate and vigorous PA due to the fear of damaging the device. A shoe-based activity monitor has been shown to accurately estimate physical activity energy expenditure in 16 adults (Sazonova et al., 2010) and could be an option for estimating energy expenditure in active participants constantly involved in vigorous physical activity.

Good agreement characterized by scores 1 to 4 was observed between B-PAR scores and RT3 VM for physical activities of light and high intensity but not for those of moderate intensity performed by the participants of the current study. Welk et al. (1998) also found an increase in VM with increasing scores but the gradient, as in the current study, was imperfect when the R3D VM

worn by children 10 to 12 years were compared to scores reported by trained research assistants. The low agreement between VM and B-PAR scores for PA of moderate intensity found in the current study may be partly due to PA intensity overestimation. Several sedentary participants overestimated their PA intensity when recording B-PAR and this may be due to their small daily PA intensity spectrum. Other limitations of B-PAR include absence of the activity performed by a participant on the list proposed by Bouchard et al. (1983) and the possibility of different PA performed over 15-min period. However, the participants were allowed to clarify any doubts arising while filling the records and to change the scores if appropriate.

The current study has some limitations. Firstly, the number of participants (11) is small but it does not seem to jeopardize the study because the difference between EE estimated by RT3 and PA records (23%) is higher than the RT3 intra-instrument coefficient of variation (6.6 to 17% depending on the intensity of PA) (Vanhelst et al., 2010). Similar studies (Jacobi et al., 2007) have included similar number of participants. Secondly, the sample of young men, mostly physical education students may have different PA patterns, compliance, awareness and understanding of EE related PA activities from the general population. Therefore, generalizability of the sample to the general population should be done with caution. A third limitation in the current study is the RT3 cut points used for 3 and 6 METs from Rowlands et al. (2004). The cut points were derived from a single sample of 15 men who performed five laboratory-based activities (sitting, kicking, hopscotch, walking and running). Thus, cut-points would be expected to differ from the free-living behaviors assessed in the current study. However, the study conducted by Rowlands et al. (2004) is the only

one that provides a relationship between METs and number of counts (VM) measured by RT3 triaxial accelerometer.

The advantages of the current study include the RMR measurement and the estimation of time and EE not recorded because the participant was not wearing the accelerometer. While other studies have shown that the estimated EE recorded by accelerometer is lower than that estimated by double labelled water (Wickel et al., 2006; Jacobi et al., 2007), this study was able to identify that the missed recorded EE estimated by RT3 was mainly during vigorous activities. Another strength of the current study is that practice guidelines and research recommendations for accelerometer use in physical activity (Ward et al., 2005) were adopted including: (a) triaxial rather than monoaxial accelerometer; (b) trunk location; (c) four days including weekdays and weekends; (d) checking monitor for accurate data output before and after each use; (e) ensured compliance (84% of the time awake wearing accelerometer); and (f) determination of light, moderate and vigorous PA bouts of 15-min periods for each participant.

In summary, this study quantified the EE not recorded by the accelerometer due to participant not wearing the device and identified that most of this energy not recorded was expended performing vigorous PA.

Conclusion

Daily EE estimation was on average 23.6% higher using the B-PAR than the RT3. The accelerometer was worn from 67 to 98% of the waking hours but up to 30% of the EE was not recorded due to the device not being worn by participants, mainly while performing vigorous PA. Recording the PA when the accelerometer is not being worn would provide a more precise estimative of the EE.

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Full Length Research Paper

Equity of care: A comparison of National Health Insurance Scheme enrollees and fee-paying patients at a private health facility in Ibadan, Nigeria

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This study compared the cost and process of care for patients enrolled in the National Health Insurance Scheme (NHIS) to those who made out-of-pocket payments for health care. A cross-sectional analytical study design was used. Data were obtained from case files of patients. The study was conducted at a privately owned general hospital in the city of Ibadan, Southwest Nigeria. A total of 200 NHIS enrollees and 200 fee-paying patients seen between January and March 2010 were recruited using a systematic sampling technique. Differences in the cost and process of care was determined by comparing cost, diagnostic process, and treatment of common ailments. Associations were explored with the chi square test, mean were compared with t-test. Level of significance was set at 5%. Only 15% of the NHIS enrollees had a diagnostic test done compared with 28.5% of the fee-paying group ($P < 0.05$). Overall, the mean cost of care was $\$14.2 \pm 5.12$ ($\text{N}2,135 \pm 772$) for the NHIS enrollees and $\$18.6 \pm 6.1$ ($\text{N}2,796 \pm 914$) for their fee-paying counterparts ($P < 0.001$). This study, indicates that some disparity exists in the cost and processes of care for these two categories of patients. It is important to ensure quality in the services received by the NHIS enrollees.

Key words: Cost, care, health, out-of-pocket, insurance, fee.

INTRODUCTION

The National Health Insurance Scheme (NHIS) was introduced in Nigeria in 2005 due to the increasing concern about the ability of the poor to afford basic health services in Nigeria (NHIS, 2006). It is the opinion of the Nigerian government that the NHIS will probably solve the problem of inequality in the provision of healthcare services and helps to improve the accessibility to health-care like some developed countries (Rice and Smith, 2001).

The Nigerian NHIS was structured to cover all groups in the society. However, the NHIS only covers federal government employees and the coverage level is less than 5% of the general population (NHIS, 2011). The

federal government employee, their spouse and four biological children are enrolled into the scheme. Enrollement with a primary care provider is mandatory to enjoy the privilege of receiving care without making payment or at least make a 10% payment of the cost of care (NHIS, 2006). The most prevalent form of health care financing in Nigeria remains out of pocket expenditure (Soyibo, 2009).

The effects of health Insurance on the quality of health care are unclear (Ekman, 2004). It is not certain whether or not equal level of care is received by NHIS enrollees and those making out-of pocket payment for health care. Also, the qualities of care received by NHIS enrollees in Nigeria have been queried (Ibiwoye and Adeleke, 2008; Acha, 2010).

The health services provided to NHIS enrollees is yet to be evaluated in comparison with the services provided to patients making out-of-pocket expenditure for health

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Table 1. Socio-demographic characteristics of patients by category.

Variable	NHIS enrollee n (%)	Fee paying clients n (%)	Chi-Square	P-Value
Age (years)				
1-18	57(28.5)	37(18.5)	9.414	0.009
19-60	142(71.0)	156(78.0)		
>60	1(0.5)	7(3.5)		
Sex				
Male	109(54.5)	92(46.0)	2.890	0.089
Female	91(45.5)	108(54.0)		
Marital status				
Married	129(64.5)	90(45.0)	15.345	<0.001
Single	71(35.5)	110(55.0)		
Occupation				
Civil servant	140(70.0)	21(10.5)	196.047	<0.001
Trader/business	0(0.0)	77(38.5)		
Student/pupils	60(30.0)	72(36.0)		
Technician	0(0.0)	30(15.0)		

care. To the best of our knowledge, no study has been done in Nigeria to compare these two categories of patients. This study therefore aimed to determine equity in the care of NHIS enrollees and fee paying patients at a private health facility in Ibadan using patients records of care. Findings from this research will be useful to know if any inequality exist in the cost and processes of care of NHIS enrollee and patient making out of pocket payment. This will assist NHIS program managers and policy makers in designing better level of care.

METHODS

The study design is cross-sectional. This study also has some analytical component. Data were obtained from case files of patients who came for out patient care. The study was conducted at a privately owned general hospital in the city of Ibadan, Southwest Nigeria. The hospital was selected using simple random sampling method among other privately owned health facilities in Ibadan, Nigeria. The hospital is registered as an NHIS health service provider. High volume of both NHIS patients and other patient making out-of-pocket payment are seen in the hospital.

A total of 200 NHIS enrollees were seen as out patient between January and March 2010 in the hospital. However, among the fee-paying patients, 1,200 patients were managed on out-patient basis. A total survey of all the NHIS patients was done, while, the fee paying patients were recruited using a systematic random sampling method to select 200 out of 1,200 patients. Hence, equal number of patients were studied in both NHIS and fee-paying patient categories. In all, 400 patients were studied. Patient admitted were excluded from the study.

The socio-demographic characteristics of patients, the common ailments which they sought medical attention for were extracted

from the patient's case notes. The cost of consultation, investigations, drugs and other consumables used for each patient was documented by the hospital's account officer for both categories of patients. The cost of care and process of care (using diagnostic and treatment procedures only) for uncomplicated cases of specified illnesses were the outcome measures for the study. A dollar was equivalent to ₦150 when the study was done.

Data was collected using a proforma, cleaned, entered and analyzed using SPSS version 15. Chi-square test was used to explore association between variables of interest. Differences were also determined in the average cost of treatment of NHIS enrollees and fee paying patients. Mean cost of care between patients in the two categories was compared using t-test. Level of significance was set at 5%. Permission to carry out the study was obtained from the medical director of the hospital after careful explanation of the purpose, content and implication of the research.

RESULTS

Table 1 shows the socio-demographic characteristics of the patients by category. Significant differences were observed in the age, marital status and occupation ($p < 0.05$). The NHIS enrollees were younger than the fee paying clients. More NHIS enrollees were in the dependent age category of 1 to 18, 57(28.5%) against fee paying patients 37(18.5%). Other socio-demographic variables are as shown in Table 1.

Table 2 compares the mean cost of care for the common ailments, treatment of malaria cost \$18.85 (₦2,827.38) among the fee paying patient compared with \$15.4 (₦2,309.44) among NHIS enrollees ($P = < 0.001$). The mean cost of care of respiratory tract infection also differ

Table 2. Comparison of common ailments and mean cost of care per patients category.

Diagnosis/treatment category	Category of patients	n	Mean± SD (₦)	Standard deviation	T-test	P-value
Malaria	NHIS	90	2309.44	641.929	4.919	<0.001
	Fee for service	84	2827.38	745.808		
Respiratory tract infection	NHIS	23	1852.17	593.809	6.109	<0.001
	Fee for service	16	2962.50	501.830		
Hypertension	NHIS	19	2342.11	818.071	1.717	0.097
	Fee for service	12	2850.00	775.183		
Trauma/injury	NHIS	6	1483.33	40.825	3.563	0.002
	Fee for service	18	3261.11	1203.983		
Skin infection	NHIS	18	2261.11	1207.885	0.889	0.383
	Fee for service	7	1842.86	377.964		
Peptic ulcer disease	NHIS	6	2100.00	1127.830	-0.869	0.399
	Fee for service	11	2736.36	1576.878		
Muscular pain	NHIS	18	1600.00	289.015	-3.103	0.004
	Fee for service	24	2212.50	796.903		
Anxiety disorder	NHIS	2	1550.00	494.975	-3.940	0.008
	Fee for service	6	2200.00	0.000		
Arthritis/osteoarthritis	NHIS	8	1800.00	320.713	-11.645	<0.001
	Fee for service	2	4600.00	141.421		

Table 3. Comparison of overall mean cost of care.

Category of patient	n	Mean cost (₦)	Standard deviation	T-test	P-value
NHIS enrollee	200	2134.75	772.29	7.813	<0.001
Fee for service	200	₦2795.95	914.31		

differ significantly \$12.35 (₦1,852.17) for NHIS enrollee and \$19.75 (₦2,962.50) for fee paying patient ($P<0.001$). Trauma/injury patients among the NHIS enrollee spent \$9.9 (₦1,483.33) while fee paying patients spent \$21.75 (₦3,261.11) ($P=0.002$). Average cost of care of patients treated for skin infection was higher among the NHIS enrollee. However, the differences were not statistically significant.

Table 3 shows the comparison of overall mean cost of care of all the patients in the two categories. The mean cost of care of the NHIS enrollee was \$14.23 (₦2134.75±72.29) while that of fee paying patients was \$18.6 (₦2795.95±914.31) ($P<0.001$).

Table 4 shows the comparison of types of drugs prescribed by patient's category. Most of the NHIS enrollees had generic drugs 140(70.0%) while only 50(25.0%) of the fee paying group had generic drugs. Branded and generic drugs were dispensed to most of the fee paying group 128 (64.0%) with only 30(15.0%) to the NHIS enrollee ($P<0.001$). The pattern of request for investigation is as shown in Table 4. Only 30(15.0%) of the NHIS enrollee were asked to go for any form of test while a larger proportion of the fee paying patients 57(28.5%) had some forms of investigation ($P=0.001$).

Follow up visit was requested for a larger proportion of the fee paying patients 82(41.0%) while less proportion of

Table 4. Comparison of patient management processes by patients category.

Parameter	NHIS enrollee n (%)	Fee paying clients n (%)	Chi-Square	P-Value
Brands of drugs prescribed				
Branded	30(15.0)	22(11.0)	11.93	0.003
Generic	140(70.0)	50(25.0)		
Branded and generic	30(15.0)	28(64.0)		
Investigation requested				
Yes	30(15.0)	57(28.5)	10.708	0.001
No	170(85.0)	143(71.5)		
Follow up visit				
Yes	51(25.5)	82(41.0)	12.267	<0.001
No	149(74.5)	118(59.0)		

NHIS enrollees were given appointment for follow up 51(25.5%) ($P < 0.001$).

DISCUSSION

A health system is equitable if medical care is distributed based on patients' need as judged by health professionals (Van Doorslaer et al., 1993). The level of care a patient receives should be determined by the level of need. Equity in the level of health care is therefore, important not only in the structure and the process of care, but also in the outcomes of care (Donabedian, 1992). The NHIS aims to improve access to quality healthcare for all Nigerians at an affordable cost through a prepayment system by all beneficiaries (NHIS, 2006). The quality of care received by the enrollee of the scheme therefore needs to be comparable or even better to their counterpart who made out of pocket payment for health care.

This study shows that the mean cost of care for the NHIS enrollees were lower than the cost of care incurred by fee paying patients treated for the same condition. A higher proportion of NHIS enrollees was given generic drugs. Likewise, more patients making out-of-pocket payment were asked to carry out investigation. The benefits derivable to participants and their dependants include the use of prescribed generic drugs and diagnostic tests (NHIS, 2006). The use of generic drugs and fewer requests for investigation contributed to the low cost of care among the NHIS enrollee.

Although the lower cost of care incurred by NHIS patient might be an objective of the scheme (Monye, 2006), concerns arise about the higher numbers of investigations and follow up appointments prescribed for fee paying patients when compared with the NHIS

enrollees. In patient been treated for the same disease condition, wide disparity is not expected in the cost of care, if the same processes was utilised and treatment done with similar drugs.

These practices seem to imply that fee paying patients are getting more attention than NHIS patients. The quality of care is also being compromised for NHIS patients when compared to fee paying patients.

Conclusions

This study indicates that disparities exist in the processes and cost of care of NHIS enrollee and fee paying patients. Fee paying patients are also getting more attention than NHIS enrollee. Before the commencement of the scale-up of the NHIS, it is important to ensure quality in the services received by the enrollees. There is therefore need to develop standard tool for collecting quality of service data; such tool should include outcome of care, adherence to best practices, organisational measures and enrollees satisfaction with the care received.

LIMITATIONS

The outcome of care of the patients whose records were used was not known. It would have been a better indicator for measuring quality of service received. Another limitation is that NHIS offer equal benefit to all its enrollee receiving primary care, while benefit of fee paying patients may be determined by the amount of money they can offer for services rendered. Though, it was not known if the patients were healthier in one group versus the second. Significant difference was however, not expected. Also, only a very small share of the

population of Nigeria (5%) is covered by the National Health Insurance Scheme whose efficiency is studied and hence, to form a representative sample of that group is certainly not as easy as to form a corresponding sample from those paying out of the pocket.

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Full Length Research Paper

Results of a peer navigation pilot program to link HIV positive clients of harm reduction services with Ryan White Clinical Service Providers

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Peer navigation programs may improve healthcare accessibility and adherence for hard-to-reach populations. We piloted a peer navigation program at 3 sites within the United States with the aim of linking HIV positive clients of harm reduction services with Ryan White Clinical Services. We compared navigator activity logs and client tracking forms to evaluate the efficacy of the peer navigation program and to determine whether specific navigator duties varied with instances of client navigation. Findings indicated that increased instances of peer navigator activities corresponded with successful navigation of clients. Peer navigation may be a promising model for overcoming barriers to healthcare access for hard-to-reach populations.

Key words: HIV care, peer navigation, Ryan White services, drug use.

INTRODUCTION

While the prevalence of HIV has declined among drug users in the United States, drug users living with HIV continue to face problems accessing treatment and services for HIV. The Ryan White HIV/AIDS Program Clinical Services provides services for many drug users living with HIV; however, barriers such as variable rates of testing, delayed testing and diagnosis, and general healthcare accessibility continue to impact the ability of drug users to access these services (Grigoryan et al., 2009; Lansky et al., 2009). One possible strategy for linking the hard-to-reach population of HIV positive drug users to care is through the use of peer navigation.

Often described as a health-systems intervention, *peer navigation* aims to improve healthcare accessibility and adherence for hard-to-reach populations, or potential clients of healthcare services (Bradford et al., 2007), by providing the client with navigation through the complexities of healthcare. Unlike case management, peer

navigation utilizes peers who share common characteristics with patients (which may include race, gender, age, HIV status, etc.) to build relationships with patients and link patients to care. This model of navigation is considered a health-systems level intervention as it often necessitates hiring new staff and/or training existing staff to assume new roles as peers within healthcare facilities.

The present research endeavor is an evaluation of a pilot peer navigation program implemented in three sites in the United States from 2009 to 2010. Our central research aims were to: (1) Assess the overall efficacy of the peer navigation program in linking HIV positive users into care; and (2) Identify the relationship between specific navigator occupational duties and instances of patient navigation.

METHODS

To examine the relationship between navigator activities and patient navigation, we used archival data to build a database which indicated navigator activities over time, measured in weeks. Seven patient navigators working at three sites maintained weekly activity

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Table 1. The odds of navigation given peer navigator activities, fixed effects model with random intercepts for peer navigators, controlled for relative time period.

Peer navigator activity	Instance		P value	Fixed effects intercept estimate (SE)
	Adjusted odds ratio	95% confidence interval		
Number of instances of navigator				
Communicating with Ryan White Services point-contact	1.3	1.1-1.7	0.013	0.58 (0.49)
Provided navigation into harm reduction services	1.4	1.1-1.8	0.005	1.15 (0.56)
Making community contacts	0.98	0.96-1.01	0.301	0.96 (0.57)
Used telephone for navigation-related activities	1.3	1.1-1.5	0.001	0.87 (0.51)
Provided patient education	4.3	2.1-8.8	<0.001	0.0 (2.1)

logs which documented instances of navigator duties across the following occupational domains: The number of instances that navigation was provided into Ryan White services, communications with Ryan White services point of contact, number of instances that navigation was provided into harm reduction services, number of community contacts, number of telephone calls made for navigation, number of unduplicated clients served, and number of clients for whom education was provided. For each week, a navigator reported the number of instances they engaged in a given occupational domain specific to navigation; thus not engaging in an occupational activity would receive a frequency of 0 in comparison to a domain for which activities were reported (≥ 1 instance), and were individually treated as count variables. To ensure that a patient was navigated during the week reported in the navigator activity log, we cross validated the time period from the navigator logs with the patient tracking logs that were maintained by the Ryan White Services case worker. The variable representing whether navigation occurred was coded binomially (0, 1) to represent weeks in which navigation occurred (0=time period in which navigation did not occur, 1=time period in which navigation did occur).

Quantitative data were analyzed using STATA 10 analytic software ("Stata 10", 2007). Means and standard errors were examined for tracking peer navigator program activities. Two tailed T-tests were used to examine mean differences between groups. In order to model the binomial outcome (of whether a patient had been navigated during a specific time period), we used fixed effects models to generate adjusted odds ratios (aOR), and adjusted for inter-navigator variability (in the intercept) and time of observation.

RESULTS

In total, navigators identified and navigated 20 clients into Ryan White Clinical Services. Among patients navigated, 53% were male and 47% were female; 75% were 25 to 44 years old and 25% were 45 to 64 years old; 15% identified as being of Hispanic or Latino origin; 10% as Asian, 70% as Black or African American, and 5% as White/Caucasian.

Across navigators and sites, the peer navigation program resulted in a cumulative total of: 42 novel navigation engagement attempts made by navigators; 26 new clients for whom at least one navigation attempt was made; 172 instances of navigator communication with the Ryan White services point-contact; 177 instances of navigation provided into Harm Reduction services; 3,085

instances of community contacts; 290 navigation related telephone calls; 573 new client orientations conducted; and 212 clients for whom education was provided.

Results in Table 1 exhibit that instances of navigator-specific activities corresponded with instances of patient navigation. Results indicate that periods in which a patient was navigated corresponded with an increase in patient navigators communicating with Ryan White services points of contact (aOR=1.3), making telephone calls (aOR=1.3), providing patient education (aOR=1.3), and navigating patients into harm reduction services (aOR=1.4).

Quantitative results point to the efficacy of peer navigators in recruiting and navigating hard-to-reach, predominantly ethnic minority drug users into Ryan White services. Increases in navigators' instances of communication with drug users were associated with increases in the number of users linked to services, reported navigation activities, in the number of users navigated into care, peer navigators increased their communication and telephone calls during periods of navigation, suggesting that first, the model exhibited success in recruiting and navigating hard-to-reach, predominantly ethnic minority drug users into Ryan White services. Peer navigators increased their communication and telephone calls during periods of navigation, suggesting that their devoted role as peer navigators was beneficial to the navigation process.

DISCUSSION

Providing stable HIV care services for active drug users is a challenging task. Research on harm reduction interventions surrounding drug users aims at enrolling drug users into harm reduction programs and reducing HIV transmission risk (Des Jarlais et al., 2007; Finlinson et al., 2008; Li et al., 2007; Mesquita et al., 2008; Miller et al., 2006). While this approach targets a low-threshold of behavior change for drug users in line with the harm reduction model, the navigation of HIV positive clients into Ryan White services is an additional step which can

ensure access to treatment and care services for HIV positive clients. This is not to be taken lightly. In one study of regular heroin users in Australia, it was found that 35% were not engaging in overdose prevention practices, and common interview themes included indifference toward life, death as an occupational hazard of drug use, and death as a welcome relief (Miller, 2009). Indeed, low-threshold measures of behavior change, such as entry into HIV clinical services, can represent a comparatively large change in behavior from the perspective of certain drug using populations. This reflects the need for a devoted patient navigator to address the array of client issues which arise in attempting to bridge a healthcare accessibility gap for HIV positive drug users.

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Full Length Research Paper

Giant aortic arch thrombus, methylenetetrahydrofolate reductase (MTHFR) A1298C heterozygous gene mutation, smoking and hormonal replacement therapy

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We report the case of a mobile aortic arch thrombus possibly induced by the combination of postmenopausal hormonal replacement therapy (HRT) and cigarette smoking in a woman with methylenetetrahydrofolate reductase (MTHFR) A1298C mutation. No other cause for her illness could be identified despite an extensive laboratory work-up for thrombophilic state. Surgical exploration showed the floating aortic arch thrombus attached on a histologically normal aortic wall. At an 8-year follow-up, she remained free of recurrence after discontinuation of HRT and counseling to quit smoking. The probable synergistic impact of tobacco smoking as an additional risk factor for thrombophilic events in women with MTHFR variant and using HRT has yet to be determined. Previous studies and case reports focusing on MTHFR variation and the incidence of thrombotic events have provided conflicting evidence of an association. With the understanding that this case does not yet ascribe cause-and-effect relationship between MTHFR variant and clot formation, important public health concerns are raised. The prevalence of MTHFR A1298C genotype is population-specific, implying that permissive gene-environment interactions other than genetic mutation alone may also be relevant in establishing a clinically overt disease. Causality remains to be proven in prospective evaluation across diverse geographic areas taking into account interactions with dietary and other life-style risk factors. Furthermore, in such genetically predisposed patients, future genome-wide association studies to identify loci variants that determine the overall susceptibility to thrombosis may prove helpful to derive preventive interventions.

Key words: Aortic arch thrombus, hormone replacement therapy, methylenetetrahydrofolate reductase (MTHFR) A1298C gene mutation, smoking.

INTRODUCTION

Thrombus formation in aortic arch is a devastating condition. Herein, we present such a case that was associated with methylenetetrahydrofolate reductase (MTHFR) A1298C genetic variant and normal homocysteine level. Does heterozygous MTHFR A1298C

allelic gene mutation without hyperhomocystenemia increase arterial thrombophilia? The answer to this question remains a subject of debate. The etiology of increased tendency to clotting is thought to be a multigene disorder (Seligsohn and Zivelin, 1997; Ehrenforth et al., 2004; Sacher, 1999), making this genotype variant as a cause of thrombus formation difficult to ascertain. Furthermore, such genetic variation is ethnic and population specific. For example, the overall prevalence of this allelic variant in population-based

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Figure 1. Transesophageal echocardiography long-axis view of the aortic arch showing large mobile thrombus along aortic wall.

United States (US) survey was 28.4% (Chang et al., 2009). In that study, the incidences across racial categories were 31.1, 17.9 and 18.8%, in White, Black, and Mexican American, respectively. In contrast, a study reported by Saltanpour et al. (2011) found the MTHFR allele in more than 38% of Iranian subjects irrespective of the presence of venous thrombosis.

The most common missense mutation identified in the MTHFR gene is the C to T substitution (C677T). Deficiency in this gene, an autosomal recessive disorder, leads to a reduced enzymatic function with a mild hyperhomocysteinemia and coronary artery diseases. Hyperhomocysteinemia has an important role in inducing hypercoagulability state on the venous system in the general population (Den Heijer et al., 1996). However, arterial clot formation in the less common heterozygous allelic mutation MTHFR A1298C has thus far not been reported. In this report, the role of the gene-environmental interaction for vascular damage in case of MTHFR mutation is also highlighted.

METHOD

Case presentation

A 51-year-old female presented with multiple recent bilateral cere-

bellar infarcts and found to have heterozygous methylenetetrahydrofolate reductase MTHFR A1298C. For three months prior to admission, she had been on oral daily postmenopausal HRT for symptoms control. Each tablet contains norethindrone acetate, ethinyl estradiol (1 mg/ 5 mcg). There was no personal or family history of venous or arterial thrombotic disease or coronary artery disease, hypertension, diabetes mellitus or hyperlipidemia, and she has never been on oral contraceptives.

The patient had no history of weight loss, trauma, and no clinical manifestations of inflammatory bowel disease, malignancy, cutaneous ulcers or nodules, tuberculosis, syphilis or vasculitis. She had 13 pack-years history of cigarette smoking and did not drink alcohol or use illicit drugs.

Transthoracic and transesophageal echocardiography demonstrated a large soft mobile echogenic mass with an irregular shape visualized in the aortic arch with absence of intramural hematoma (Figure 1). The heart rhythm, ventricular function and the cardiac valves were normal and no intracardiac source of emboli was identified. With the risk of embolization, and absence of angina symptoms, coronary catheterization was thought to be unwise and therefore was not performed. Computed tomography scans of the head, abdomen and pelvis did not reveal evidence of malignancy. The carotid ultrasound was unrevealing. Results of laboratory evaluation showed normal platelets count and no abnormalities of coagulation factor II, or V, and normal levels of protein C, protein S, and antithrombin III; tests for complement, anticardiolipin antibodies and lupus anticoagulant also yielded negative results. The erythrocyte sedimentation rate and the thyrotropin level were normal. Subsequent screening for thrombophilic state showed heterozygous mutation in gene encoding for 5, 10-methylenetetra-

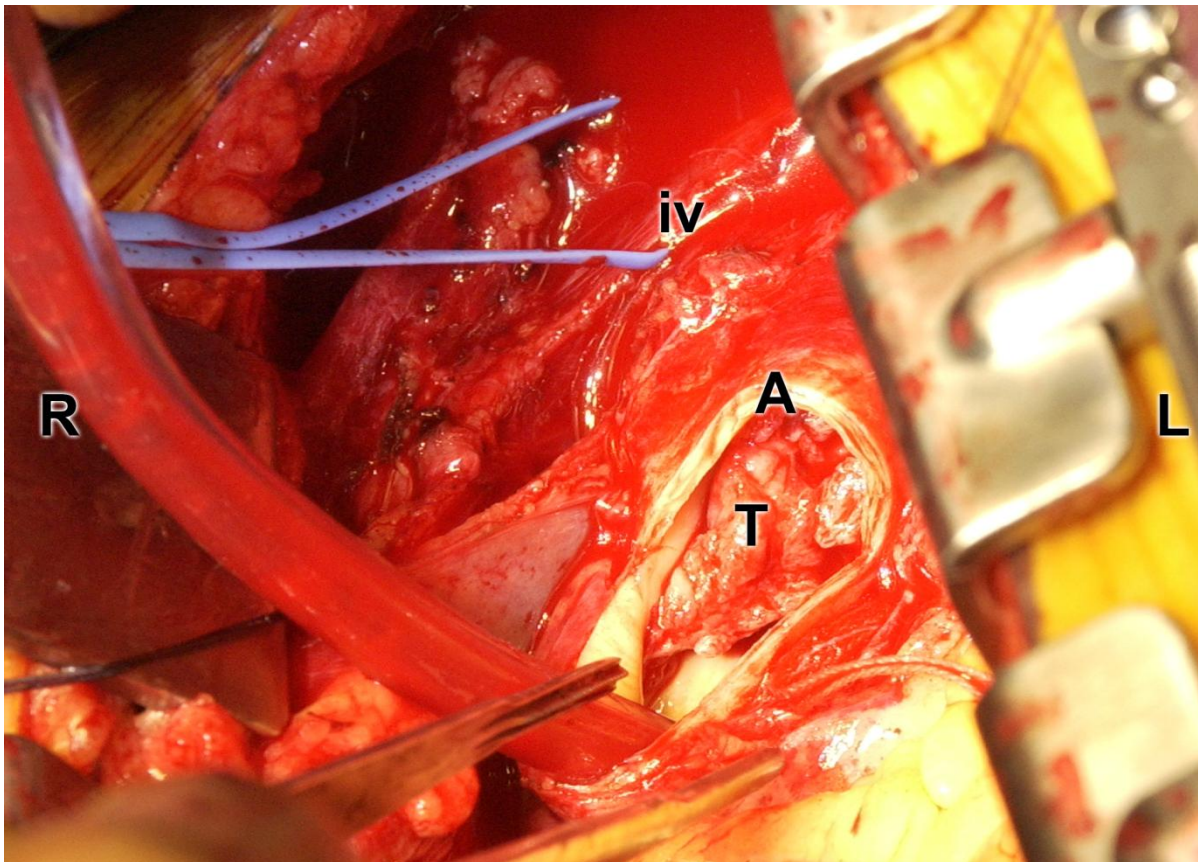


Figure 2. Intraoperative image of the thrombus in the aortic arch. iv, innominate vein; T, thrombus; A, opened aortic arch; R/L, right and left side of the patient).

hydrofolate reductase (MTHFR) A1298C without hyperhomocysteinemia.

Thrombolysis of the clot could not be undertaken because of risk of partial lysis or dislodgment of the thrombus, therefore urgent surgical intervention was indicated to prevent fatal thromboembolic events. Exploration via a midsternotomy revealed a friable thrombotic mass measuring 3.5 × 4.0 cm, localized in the aortic arch and prolapsing outward into the distal aorta beyond the innominate artery (Figure 2).

Excision of a small button of the aortic wall surrounding the thrombus and local patch graft repair were performed. Histopathologic examination revealed a thrombus attached to a normal aortic wall with the absence of protruding atherosclerotic plaque ulcerations or malignancy at the site of insertion of the thrombus (Figure 3).

RESULTS

The patient was discharged home 6 days postoperatively after an uneventful recovery on a regimen of aspirin and folate after discontinuation of HRT and advised smoking cessation. The role of long-term anticoagulant therapy in the treatment of idiopathic arterial thrombosis is controversial, but antiplatelet agents have been shown to be effective in the prevention and treatment of arterial

thrombosis (Guidelines for the Primary Prevention of Stroke, 2011; Baigent et al., 2002). The patient continues to do well at 8 years of follow-up and she reported no further episodes of cerebral infarcts. After that last visit to her internist, the patient moved out of state and was lost to follow-up.

DISCUSSION

The mechanism underlying aortic thrombus formation is complex and likely multifactorial. Aortic atheroma (plaque thickness ≥ 4 mm, ulcerated or with mobile component, is an important non-cardiac source of peripheral or cerebral emboli (Aldons, 2000). There is a lack of data showing direct association between MTHFR A1298C and arterial thrombus formation. Although heterozygous mutation in the gene encoding MTHFR have been identified in this patient, it remains uncertain whether this genetic polymorphism without hyperhomocysteinemia can cause thromboembolic events in the arterial system (Spiroski et al., 2008; Spiroski et al., 2008; Trabetti, 2008; Schwahn and Rozen, 2001; Contractor et al., 2011; Domagala et al., 2002; Kim and Becker, 2003).

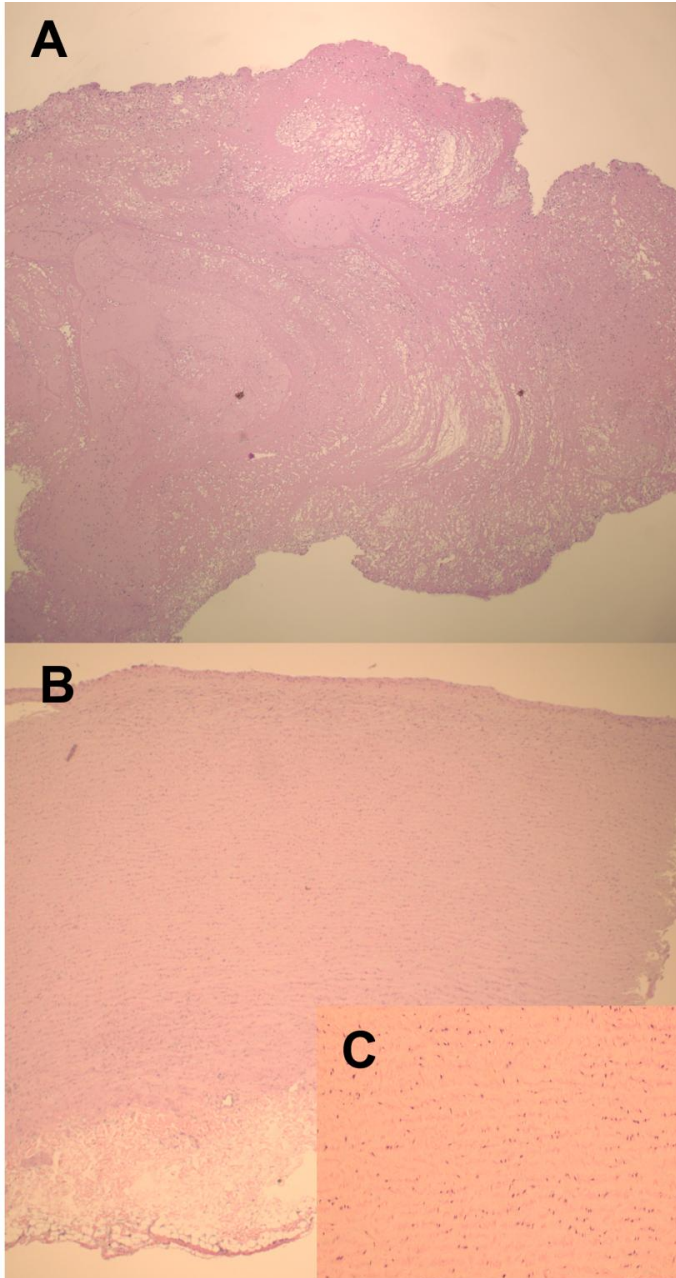


Figure 3. On microscopical examination (hematoxylin and eosin) the aortic wall has no underlying atheromatous plaque. The aortic luminal thrombus (A) was focally adherent to the aortic wall (B). Magnification of the aortic wall (inset C) showed minimal mucinous degeneration without atherosclerotic plaque or other abnormality.

Since this patient had no other cause for her clotting disorder that could be ascertained, a synergistic effect of smoking, estrogen intake, along with her genetic profile may have contributed to her arterial thrombotic event through a loss of endothelial protection, enhanced activity of thromboxane A_2 , and initial platelet activation (Leone, 2007; Pretorius et al., 2010; Khullar and Maa, 2012; Herrington and Howard, 2003; Petitti, 2012).

Role of HRT and smoking in arterial thrombosis

There are indirect estimates of postmenopausal women smokers on HRT in the US general population. According to data drawn from national information sources (Third National Health and Nutrition Examination Survey, conducted in the US between 1988 and 1994), an estimated 37% of postmenopausal women took HRT pills for 1 to 5 years (Women-Health Facts, 2012).

Interestingly, the prevalence of smoking in the US has decreased; however, an estimated 17.4% women continued to smoke in 2007 (Women-Health Facts, 2012). With such a large number of women smokers using HRT, a minute increase in prothrombotic states brought about by other frequent risk factors for thrombophilia such as overweight or obesity, inflammation, malnutrition, malignancy and factor V Leiden, will affect many (Nelson et al., 2012; Cushman et al., 2004; Miller et al., 2002). Multiple studies have shown a moderate increased risk for arterial thrombosis (stroke/myocardial infarction) due to HRT intake (Slooter et al., 2005; Lidegaard et al., 2012; Hannaford, 2000). Together, the data suggest that HRT increases the risk of thrombophilia. This conclusion is congruent with the recommendation by the Agency for Healthcare Research and Quality (US) which does not recommend long-term use of HRT for the same reason (Nelson et al., 2012; Miller et al., 2002; Rossouw et al., 2002).

The MTHFR mutation affects genomic methylation through an interaction with folate (Friso et al., 2002). Consequently, it interacts with multiple other factors. These factors include the genetic make-up of individual patients, geographic regions, ethnicity, associated prothrombotic or inflammatory states, dietary habits, and multiple lifestyle factors and nutritional supplementation (Zheng et al., 2000; Zhao et al., 2011; Gürsoy et al., 2011). Lidegaard et al. (2012) have reported an increased risk by a factor of 1.5 to 2 among users of oral estrogen-progestin. This risk in arterial thrombotic events could be minimized by abstinence from smoking (Hannaford, 2000).

Is MTHFR polymorphism without hypercystenemia associated with idiopathic thrombosis?

In the setting of a population-specific but prevalent MTHFR A1298C polymorphism, the effect of combining smoking and HRT raises important public health concerns in the generation of venous as well as arterial thrombi. As mentioned earlier, this conclusion is difficult to prove, mainly because of unforeseen confounding factors that influence final phenotype or so called "phenotype modifiers" (Girirajan et al., 2012; Girirajan and Eichler, 2010; Dipple and McCabe, 2000). In our case, homocysteine level was normal. However, low dietary intakes of folate and riboflavin, vitamins B_{12}/B_6 , all have been implicated to playing a role in plasma level of

homocysteine (Domagala et al., 2002; Kanth, 2011; Dawson and Waters, 1994).

Impact and prevalence of MTHFR genotype on thrombotic diathesis

Our patient was white of European heritage, and after discontinuation of both smoking and HRT intake, there were no additional reported neurological vascular events up to 8 years after discharge.

Considered in isolation, the risk of increased clotting in MTHFR mutation is still equivocal (Schwahn and Rozen, 2001; Gürsoy et al., 2011; Dölek et al., 2007). Noteworthy, based on data derived from case/control reports, genetic susceptibility to thrombosis and the prevalence of MTHFR may vary in different ethnic populations worldwide (Hannaford, 2000; Dipple and McCabe, 2000; Dawson and Waters, 1994; Gürsoy et al., 2011). A Macedonian case-control study suggested that the prevalence of C677T and A1298C genotypes are connected with increased homocysteinemia level among patients with deep venous thrombosis (DVT) (Domagala et al., 2002). In that study, Domagala et al. (2002) observed a 15% incidence of MTHFR variant in healthy Polish cohort.

According to recent literature, A1298C mutation was equally distributed in the Turkish patient group with DVT compared with the control group (Dölek et al., 2007). Similarly, the report by Solomon et al. (2001), as well as the report by Zetterberg et al. (2002) found no increase in DVT or vascular disease. A 2003 meta-analysis review and a recent study comparing patients with venous thromboembolism and healthy subjects also failed to demonstrate such a link (Domagala et al., 2002; Kim and Becker, 2003). Therefore on the basis of this case and other data, MTHFR A1298C polymorphism alone may not be sufficient to confer clinically overt thrombophilia. There must exist other permissive environmental factors leading to increase clotting propensity. Exposure to smoking and hormone replacement therapy each elicits integrated risk of increased thromboembolic events in parallel to genetically-controlled hypercoagulable response by such factor as the enzyme MTHFR. Moreover, other lifestyle factors and nutrients in the diet have been shown to interact with that enzyme. For example the findings by Huang et al. (2011) in a cross-sectional study further support that notion. In that study, of Puerto-Rican men and women residing in the Boston metropolitan area, subjects with MTHFR A→C displayed significant interactions with alcohol intake, smoking and physical activity in determining plasma homocysteine level. There have also been reports confirming interactions between genetic MTHFR variant and the risk for esophageal cancer in former moderate and heavy drinkers or smokers in the Chinese population (Zhao et al., 2011).

Similarly, recent Medline search to identify association

between MTHFR mutation and arterial circulatory events has suggested that the individual propensity for those events is due to other systemic mechanisms (Kim and Becker, 2003).

Finally and consistent with this view, association between MTHFR mutation and cerebral infarction and DVT has also been reported in the Chinese population by Zheng et al. (2000). In these cohorts of patients, the prevalence of the 677 C→T allele in normal control subjects was 30.7%, similar to that in Caucasians and Japanese.

Taken together, these data show that the prevalence of MTHFR varies among different populations and that in addition to the traditional risk factors (such as tobacco use, hypertension, dyslipidemia, HRT intake, diet and sedentary life-style) complex strong gene-gene and gene-environmental interactions form significant effects on the incidence of overt thrombotic events (Schwahn and Rozen, 2001).

What does this case inform us?

The patient's findings imply the need in maintaining a wide-ranging view of carefully assessing the genetic causes of arterial thrombotic events especially when the reason is not identified in women who are smokers and on HRT. This case also suggests that gene-environment interactions in genetic disorder confer rather very different clinical manifestations among populations that may be relevant in this and other genetic disorders.

Conclusions

The data supporting the relationship between MTHFR mutation and inclination to thrombosis are conflicting. Available clinical and epidemiologic evidence show that there is broad ethnic and regional variability in the clinical response to MTHFR polymorphism. If a link exists between smoking and HRT that predisposes female patients to arterial thrombosis in the setting of this allelic gene mutation that will certainly raise important matter in clinical practice and in public health. Specifically, is it necessary to endorse genetic testing for such mutation in thromboembolic events for risk stratification and therapeutic decisions? Perhaps, the answer to this question remains a matter of individual judgment. There may be specific subgroups of women with certain predisposition to traditional thrombotic risks who are more likely to benefit from a genetic testing for MTHFR before prescribing HRT, even if the use of HRT is intended for the short-term. Future studies of genome-wide sequencing and the interactions with environmental elements-in different geographic areas-may clarify the susceptibility to thrombophilia and may yield results that foster causal relationship. Special attention should be

given to higher thrombotic risk groups to intervene and modify risk factors.

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Full Length Research Paper

Importance of diet on disease prevention

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Over the last decades, a considerable body of evidence supported the hypothesis that diet and dietary factors play a relevant role in the occurrence of diseases. To date, all the major scientific associations as well as the World Health Organization, scientific and non-scientific organizations place an ever-increasing emphasis on the role of diet in the strategies able to prevent noncommunicable diseases. Many studies have evaluated the associations between food groups, foods, or nutrients and chronic diseases, and a consensus about the role of nutritional factors in the etiology of noncommunicable diseases such as cardiovascular and neoplastic diseases has gradually emerged. Indeed, data from analytical and experimental studies indicated a relation between increased consumption of some food categories such as fruits and vegetables, fiber and whole grains, fish and moderate consumption of alcohol and reduced risk of major chronic degenerative diseases, whereas increased total caloric intake, body weight, meat and fats are associated with greater risk. However, the appropriate dietary strategy to prevent chronic degenerative diseases remains a challenging and a highly relevant issue. Recently, Mediterranean diet has been extensively reported to be associated with a favorable health outcome and a better quality of life.

Key words: Diet, nutrition, diseases, health.

INTRODUCTION

During the past decades, a rapid expansion in the number of relevant scientific fields, and in particular, the amount of population-based epidemiological evidence has clearly demonstrated the role of diet in preventing and controlling morbidity and premature mortality resulting from non-communicable diseases (NCDs) (World Health Organization Study Group, 2003).

The burden of NCDs is rapidly increasing worldwide. It has been calculated that, in 2001, chronic diseases contributed approximately 60% of the 56.5 million total reported deaths in the world and approximately 46% of the global burden of disease. Moreover, the proportion of the burden of NCDs is expected to increase to 57% by

2020 (World Health Organization, 2005). Almost half of the total chronic disease deaths are attributable to cardiovascular diseases; obesity and diabetes are showing worrying trends, whereas neoplastic diseases are still one of the commonest causes of mortality and morbidity in Western countries, as well as neurodegenerative diseases which showed in the last years an increasing trend of incidence. Moreover, the chronic disease problem is far from being limited to the developed regions of the world.

Contrary to widely held beliefs, developing countries are increasingly suffering from high levels of public health problems related to chronic diseases (World Health Organization, 2005). The World Health Organization (WHO) in its recent documents places a great emphasis on the prevention of NCDs (World Health Organization Study Group, 2003; World Health Organization, 2005, 2006). The most important risk factors for NCDs include

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high blood pressure, high concentrations of cholesterol in the blood, inadequate intake of fruit and vegetables, overweight or obesity, stress, physical inactivity and tobacco use. Five of these risk factors are closely related to diet. Indeed, unhealthy diet is among the leading causes of NCDs, including cardiovascular diseases, type 2 diabetes and certain types of cancer, and contribute substantially to the global burden of disease, death and disability.

Currently, the relationship between diet and diseases has been studied intensively for nearly a century. The first evidence of a possible relationship between dietary habits and occurrence of diseases dates back to the years following the World War II, when significant variations in the incidence of major NCDs such as cardiovascular diseases and certain cancers were observed in studies conducted in migrants that moved from countries with a favourable dietary profile to a country with an unfavourable and industrialized profile. Subsequently, many studies investigated the influence of diet and nutrition on the pathogenesis of the disease states through using analytical, ecologic and epidemiological approaches (Sofi et al., 2008).

To date, diet and nutrition are important factors in the promotion and maintenance of good health throughout the entire life course, and their role as determinants of chronic degenerative diseases is well established, thus occupying a prominent position in prevention activities.

DIET AND CARDIOVASCULAR DISEASES

Cardiovascular diseases are the first cause of mortality and morbidity in Western countries (World Health Organization, 2006). During the last decades, clinical investigation on the prevention of cardiovascular diseases has defined in an unquestionable manner, the role of diet as a modifiable risk factor. Currently, it has been largely demonstrated from epidemiologic studies that increased consumption of fruits, vegetables, non-refined cereals, and fish can reduce cardiac events and related mortality in the whole population (World Health Organization, 2005). The recent result from the "InterHeart" study, a large case-control study that investigated risk factors for myocardial infarction within 52 countries including non-developed, developing and industrialized countries, demonstrated that diet is one of the most important risk factors for the occurrence of myocardial infarction, independently from all the other parameters. In fact, consumption of fruit and vegetables has been reported to be responsible for a significant and relevant protection against the occurrence of myocardial infarction in all the countries (Yusuf et al., 2004). Furthermore, the significant interrelationships between some of the most important risk factors such as diabetes,

hypertension, and dyslipidemia and dietary habits gave further evidence towards the role of nutrition in preventing cardiovascular diseases.

The preliminary scientific evidence about the role of nutrition in the pathogenesis of cardiovascular diseases has been supplied by the "Seven Countries' Study", an epidemiologic study designed by Ancel Keys, the pioneer of nutritional studies, at the beginning of the 1950s (Keys et al., 1986). This study enrolled nearly 13,000 male subjects of age ranging from 40 to 59 years, living in 7 different countries (Italy, Greece, the Netherlands, United States, Finland, Japan, former Yugoslavia), with the aim of evaluating the possible association between diet and lifestyle habits and mortality and incidence of cardiovascular and neoplastic diseases. Since the first results of the study, it became evident that there was a significant difference in terms of incidence of diseases, as well as of mortality among the cohorts of the study. At the end of the 25 years follow-up, about one half of these death cases were due to a coronary disease with mortality rates remarkably differing in the various study countries (Menotti et al., 1993).

In particular, a lower mortality rate for coronary heart disease was recorded in Greece and in the South of Italy, with 25 death cases every 1,000 inhabitants in a 25-year period, whereas the highest mortality rate was recorded in Finland with 268 death cases every 1,000 inhabitants in a 25-year period. The low rate of cardiovascular diseases in the Mediterranean regions of Europe stimulated an increasing interest for the potential role of their traditional diet in the protection from these diseases.

From that time onward, several studies have been conducted in different study populations with the aim of identifying the real relationship between nutrients, foods, food groups and diseases, by showing that a dietary profile typical of the Mediterranean regions is associated with a reduced incidence of NCDs, as well as with a reduced rate of mortality and morbidity (Sofi et al., 2008). In the Mediterranean diet, olive oil rich in monounsaturated fatty acids is the prevalent visible fat, the intake of saturated fat is relatively low, while fish guarantees a substantial provision of polyunsaturated fats (n-3 polyunsaturated fatty acids). The Mediterranean diet is, in fact, characterized by a high amount of vegetables, fruits and whole grain products, which represent a good source of fiber, complex carbohydrates, proteins, potassium, antioxidant substances, and vitamins. Finally, the moderate consumption of red wine associated with the food is prevalent with respect to other types of alcoholic beverages.

The association between these nutrients and foods and the occurrence of cardiovascular diseases has been largely demonstrated in the last decades (World Health Organization, 2005; Sofi et al., 2008). However, the failure of several recent clinical trials supplementing single

nutrients, suggested that the global Mediterranean nutrition pattern, rather than specific nutrients, might have protective effects on cardiovascular diseases. This is in agreement with some intervention studies, main ones being the Lyon Diet Heart Study and the Dietary Approaches to Stop Hypertension trial, which indicated that interventions to change dietary patterns into a Mediterranean-like pattern could be highly effective in reducing cardiovascular risk (de Lorgeril et al., 1999; Sacks et al., 2001).

The Lyon Heart Study conducted among those with existing heart disease, found a Mediterranean-type diet high in omega-3 fatty acids reduced recurrent infarction by 70%, compared with an American Heart Association diet (de Lorgeril et al., 1999). More recently, an intervention study led by Shai et al. (2008) and published in the *New England Journal of Medicine*, reported a benefit for Mediterranean diet on reducing cardiovascular risk profile of a population of obese. The authors considered a comparison of three diet regimens with regard to the body weight of more than 200 obese subjects: a typical low-calorie diet low in fat, a Mediterranean-type diet, and a low-calorie and low-carbohydrate diet without caloric restriction. After approximately two years of follow-up, the low-carbohydrate diets were more effective in obtaining weight loss in the short-term, but the long-term benefits obtained in addition to the weight loss, which included improvement of the metabolic parameters were obtained in the subgroup of people following the Mediterranean diet (Shai et al., 2008).

However, the intervention diets in those trials were very different from common dietary patterns in Western populations. People choose foods and combinations of foods rather than isolated nutrients, and practical dietary advice to the public in terms of foods is preferred. Dietary changes may be more readily achieved if recommended foods are compatible with existing patterns of food consumption. Until recently, research efforts to identify dietary means of reducing disease risk have focused on single-nutrient interventions to affect responses in single medical conditions. Determining appropriate dietary recommendations for improved health is further complicated by the paucity of information of the clinical value and feasibility of the interactive effects of multiple nutrients consumed in combination. Recognizing that nutrients are not ingested in isolation, but rather as interactive constituents of a complete diet, much of the focus in nutrition and cardiovascular research in recent years has shifted from assessment of single-nutrient effects on medical conditions associated with increased risk to that of the effects of the total diet or dietary pattern. Therefore, research efforts in this field switched progressively to the evaluation of a score for the adherence to the Mediterranean dietary pattern, rather than to the identification of single nutrients in association

with the disease.

The most important attempt to define the degree of adherence to the Mediterranean diet has been released by Trichopoulou et al. (2003) on the frame of the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The authors established a score of adherence that takes into account the main dietary variables, divided into food groups, typical of the Mediterranean diet. This adherence score, based on food groups typically present in the Mediterranean diet (bread, pasta, fruit, vegetables, fish, legumes, moderate red wine consumption, and olive oil), gives a positive score to people who consume more than the median of the overall population for foods typical of the Mediterranean diet, and a negative score to those who consume a higher amount of foods which are not typical of the Mediterranean diet. Hence, a score of 0 represents the lowest adherence to the Mediterranean diet, while a score of 9 represents the highest adherence to the Mediterranean diet.

In recent meta-analyses, we have demonstrated that a greater adherence to the Mediterranean diet, estimated through a computational score, was associated with a reduced incidence of overall mortality (-8%), as well as of cardiovascular mortality and/or incidence (-10%) (Sofi et al., 2010, 2008).

DIET AND NEOPLASTIC DISEASES

Cancer is a major cause of mortality throughout the world, and in the developed world, it is generally exceeded only by cardiovascular diseases (World Health Organization Study Group, 2003; World Health Organization, 2005; World Health Organization, 2006). An estimated 10 million new cases and over 6 million deaths from cancer occurred in 2000. As developing countries become urbanized, patterns of cancer, including those most strongly associated with diet, tend to shift towards those of economically developed countries. Between 2000 and 2020, the total number of cases of cancer in the developing world is predicted to increase by 73%, and in the developed world, to increase by 29%, largely as a result of an increase in the number of old people.

Dietary factors are estimated to account for approximately 30% of cancers in industrialized countries, making diet second only to tobacco as a theoretically preventable cause of cancer (Key et al., 2004). This proportion is thought to be about 20% in developing countries, but may grow with dietary change. Many of the prominent hypotheses for effects of diet on cancer risk are derived from examination of the associations between dietary patterns and cancer rates in different populations around the world. It was noted in the 1970s that developed Western countries have diets high in

animal products, fat and sugar, and high rates of cancers of the colorectum, breast and prostate developing countries typically have diets based on one or two starchy staple foods, low intakes of animal products, fat and sugar, low rates of these 'Western' cancers, and sometimes high rates of other types of cancer such as cancers of the esophagus, stomach and liver. Other studies have shown that cancer rates often change in populations that migrate from one country to another, and change over time within countries.

During the last 30 years, hundreds of studies that examined the association between diets of individuals and their risk for developing cancer have been published. Some studies have investigated the possible role of Mediterranean diet and the occurrence of neoplastic diseases showing a beneficial effect of such dietary pattern in the general population. The results of recent meta-analyses published by our group clearly showed that a strict adherence to the rules of the classical Mediterranean diet determines a 6% reduced risk of incidence and/or mortality from neoplastic diseases (Sofi et al., 2008, 2010).

DIET AND NEURODEGENERATIVE DISEASES

An interest association between diet and disease states is the one related to the reduced risk of incidence of neurodegenerative diseases such as Alzheimer's and Parkinson's disease that has been observed in some recent studies (Sofi et al., 2008). Indeed, several observations hypothesised a potentially important role for diet in the prevention and occurrence of Alzheimer's disease.

The links proposed between dietary factors and neurocognitive diseases are different. Neurodegenerative diseases are characterized in their prevalent forms, by an increased oxidative stress and inflammation (Rinaldi et al., 2003). To date, oxidative stress and inflammation can be modulated and influenced by many dietary compounds, hence supporting the hypothesis that nutritional habits may play a role on the pathogenesis of Alzheimer's disease. Moreover, another possible link between diet and such diseases are that related to the presence of high levels of homocysteine, an intermediate compound of the metabolic cycle of methionine in patients affected by cognitive impairment (Seshadri and Wolf, 2003). Finally, additional interesting links between diet and neurocognitive disorders are those related to dietary fats, alcohol and inflammatory parameters (Mukamal et al., 2003; Wärnberg et al., 2009). High intake of cholesterol has been shown to increase the deposition of beta-amyloid in animal brains and high intake of fats may also determine oxidative stress. In addition, some findings in animal models demonstrated

that alcohol is a neurotoxin, so acting as a modulator of the oxidative brain damage.

In the last few years, researches on diet and nutrition in relation to the occurrence of neurodegenerative diseases have been reported with interesting findings on Alzheimer's and Parkinson's diseases (Sofi et al., 2008). In fact, a greater adherence to a Mediterranean-type diet has been shown to decrease the risk of occurrence of both Parkinson's and Alzheimer's disease. The results of our meta-analyses showed that an increase of 2 points in the adherence score to Mediterranean diet is associated with a reduction of over than 10% of the risk of occurrence of such pathologies, by demonstrating the beneficial role of diet and dietary habits in the prevention of neurocognitive disorders (Sofi et al., 2008, 2010).

CONCLUSION

There is a vast amount of literature, to date, that reports a healthy dietary habit to be one of the strongest preventive measure for the general population, as well as for the population of patients with a manifested disease. Diet is able to decrease the risk of mortality and reduce the incidence of some of the most important disease states.

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Full Length Research Paper

Retrospective incidence of wound infections and antibiotic sensitivity pattern: A study conducted at the Aminu Kano Teaching Hospital, Kano, Nigeria

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Infection continues to be a major complication of wounds with significant increase in costs, morbidity and potential mortality. Retrospective study of incidences of wound infection and antibiotic sensitivity pattern in patients that visited Aminu Kano Teaching Hospital, Kano, Nigeria, which involved the analysis of the medical records of 651 patients diagnosed from April, 2009 to September, 2010, was carried out. The medical records of the patients with wound infections showed that 77.9% of the wound sites were contaminated with various bacteria isolates, notably *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella* spp. in decreasing order of frequency. The most common infection site was surgical sites with amoxicillin, gentamicin and ceftriaxone, being the most commonly prescribed antibiotics for the treatment of resulting infections based on the culture and sensitivity results. The study shows that there is a high rate of wound infection in Kano, Nigeria.

Key words: Wound infections, retrospective studies, antibiotics.

INTRODUCTION

Human skin acts as an excellent barrier to infection, provided it is not breached. A wound is a type of injury in which the skin is torn, cut or punctured (open wound) or where blunt force trauma causes a contusion (closed wound). Wounds can further be classified as accidental, pathological or post-operative according to its nature (Collier, 2003). Certain parasites (for example, Hookworm larvae) and bacteria (*Treponema pallidum*) can penetrate intact skin, but certain primary skin infections like impetigo is caused by *Streptococcus pyogenes* or *S. aureus*, or both gain access through abrasions, as minor trauma to skin is a part of everyday life (Bhatt and Lahkey, 2007).

Infection of a wound is the successful invasion and

proliferation by one or more species of microorganisms anywhere within the body's sterile tissues, sometimes resulting in pus formation (Calvin, 1998). Development of wound infection depends on the interplay of many factors. The breaking of the host protective layer, the skin, and thus disturbing the protective functions of the layer, will induce many cell types into the wound to initiate host response (Collier, 2003). Wound infections may occur following accidental trauma and injections, but post-operative wound infections in hospital are most common. Some infections are endogenous in which infection occurs from patient's own bacterial flora such as *S. aureus* from skin and anterior nares or coliforms. Many infections are exogenous; skin and anterior nares are important sources of *Staphylococci*, spread of organisms from hospital staff and visitors occur by direct and indirect airborne routes.

At present, more than 60% of hospital-acquired infections are due to gram-negative enteric bacilli and only in

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Table 1. Gender and age distributions of patients with wound Infections in Aminu Kano Teaching Hospital.

Gender (April 2009 -September 2010)	No and percentage of samples with bacteria isolates (%)	Age (April 2009 -September 2011)	No and percentage of samples with bacteria isolates (%)
Male (n=387)	308 (79.6)	Adult (n=475)	392 (82.5)
Female (n=264)	199 (75.4)	Child (n=176)	115 (65.3)
Total (n=651)	507 (77.9)	Total (n=651)	507 (77.9)

30% cases are gram-positive cocci responsible (Bhatt and Lahkey, 2007). Organisms commonly found in infected wounds include Gram positive cocci such as *S. aureus*, *Streptococcus* spp, Gram negative bacilli mostly *Acinetobacter*, *Enterobacter*, *E. coli*, *Proteus* spp, *Ps. aeruginosa* and anaerobic bacteria such as *Propionibacterium* spp. and *Klebsiella* spp. (Taiwo et al., 2002).

The current spread of multi-drug resistant bacteria pathogens has added a new dimension to the problem of wound infections (Sule and Olusanya, 2000). This is particularly worse in resource poor countries where sale of antibiotics is under poor control (Onile, 1997). A regular bacteriological review of infected wounds is therefore a necessity if affected patients must receive qualitative health care, particularly when blind treatment is a necessity, as in underdeveloped and developing nations (Fadeyi et al., 2008).

This study aims at investigating the incidence of wound infection and the antibiotic sensitivity pattern at the Aminu Kano Teaching Hospital, Kano, Nigeria.

MATERIALS AND METHODS

Study area

This study was carried out at Aminu Kano Teaching Hospital, Kano in North West Nigeria. It is the largest Tertiary Health Institution in Kano State. It has a bed capacity of four hundred and twenty two.

Ethical considerations

Written Ethical approval for this study was obtained from the Medical Advisory Committee of the Teaching Hospital.

Data collection and sample size

Method of data collection was by Review of Records. A 17 months retrospective study of patients diagnosed with wound infections was carried out. A total of 651 patients were recorded over this period at the medical records department. Relevant data such as age, sex, aetiology of wound were obtained. Results of culture and sensitivity carried out by the microbiology department using standard biochemical tests were also obtained from the patient's medical records.

Statistical analysis

Medical records data was used for analysis. Data was organized in Microsoft excel and the general descriptive analysis and correlation coefficient was used to analyze occurrence and extent of factors and the statistical relationship using Microsoft excel and statistical package for social science (SPSS) windows 16.0 (Standard Version SPSS Inc., Chicago, IL, USA).

RESULTS

Out of the 651 wound samples received at the General Culture bench of the Microbiology Department of Aminu Kano Teaching Hospital from April, 2009 to September, 2010, 484 representing 74.35% yielded single organism, 23 (3.53%) yielded two organisms while 144 (22.12%) yielded no growth. The gender distribution amongst the 507 samples that showed growth, 308 (79.6%) were males, while 199 females also had almost equal proportion (75.4%) with the males. The age distribution of patients with wound infections in Aminu Kano Teaching Hospital with 392 (82.5%) being adults (from 13 years and above) and 115 (65.3%) being children (5 to 12 years) is shown in Table 1.

The percentage distribution of isolates from the different wound sites showed that the Surgical site wounds which amounted to 199 (39.9 %) of the isolates was found to be the most commonly infected. This was closely followed by wound sepsis 130 (26.1 %). All acute soft tissue infections such as road traffic accidents, lacerations, domestic violence and gunshot injuries were classified under wound sepsis and then burn sites. Infections at diabetic and non-diabetic ulcer sites were least frequent (Figure 1).

Distribution of bacteria pathogens isolated from wound sepsis site presented in Figure 2, showed that *S. aureus* is the most prevalent organism in this site, accounting for almost 60% of the isolates.

It was observed in Figure 3, that *S. aureus* constituted the most common isolate from burn sites with 63.5% frequency, followed by *E. coli* and *Ps. aeruginosa*, with 12.5 and 9.6%, respectively. *Klebsiella* spp., *Pr. mirabilis* and *Streptococcus* spp. were less frequently isolated. As depicted in Figure 4, *S. aureus* was also the most frequently isolated organism from non-diabetic ulcers,

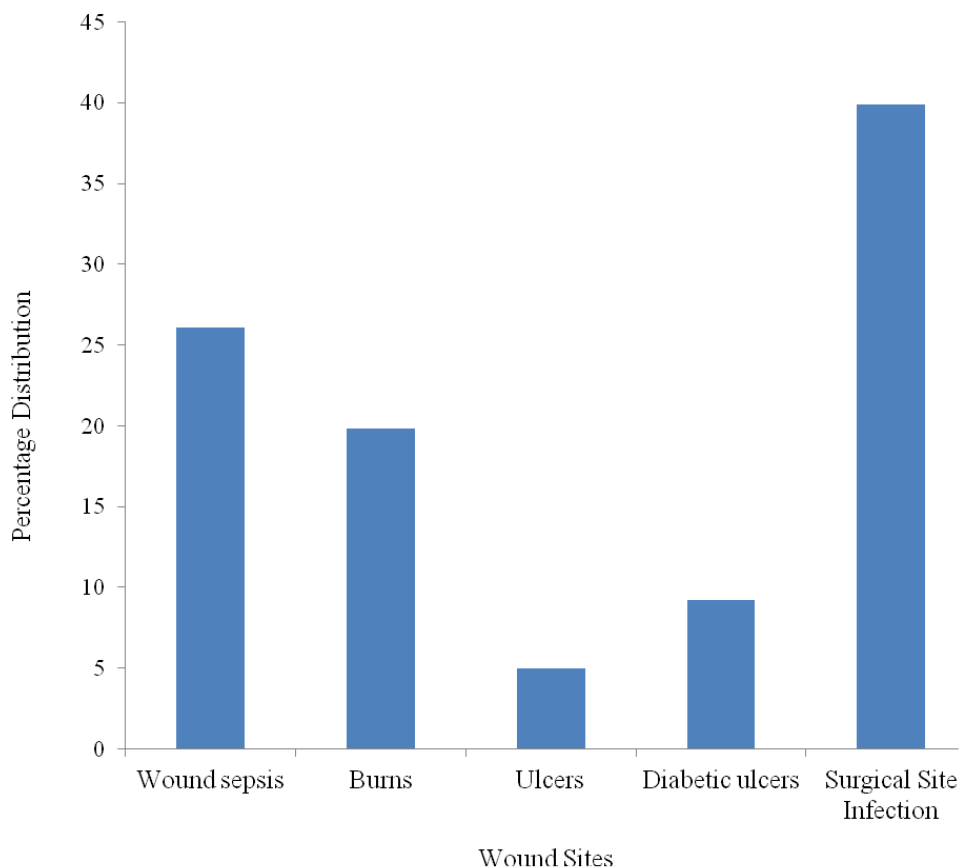


Figure 1. Percentage distribution of isolates from different wound sites of patients attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010.

accounting for 50%, followed distantly by *E. coli* and *Ps. aeruginosa*.

The most frequently isolated organisms from diabetic ulcer sites were *S. aureus* (36.8%), *Pr. mirabilis* (26.3%), *E. coli* (19.3%) and *Ps. aeruginosa* (12.3%).

Less frequently isolated from this site were *Klebsiella* spp and *Streptococcus* spp. (Figure 5). *S. aureus* continued to be the predominant organism from the surgical wound sites, constituting about 40% of the isolates. The Enterobacteriaceae such as *E. coli* and *Pr. mirabilis* were the next most frequent, followed distantly by *Ps. aeruginosa*. Only one isolate of *Streptococcus* spp. was obtained from this site (Figure 6).

Data presented in Table 2 showed that the most commonly used antibiotics in the treatment of wound infections based on the culture and sensitivity results in the hospital were β -lactam antibiotics (Penicillins and Cephalosporins) and the aminoglycosides, followed closely by the quinolones. Tetracyclines and anti-metabolites such as sulphonamides were less prescribed; only used in infections caused by *S. aureus*.

DISCUSSION

Generally, inadequate antimicrobial treatment defined as ineffective treatment of infection is an important factor in emergence of antibiotic resistant bacteria. Factors that contribute to inadequate antimicrobial treatment of hospitalized patients include: the prior use of antibiotic, broad spectrum antibiotics, prolonged hospital stay and the presence of invasive medical devices. The relatively high percentage of wound samples with infection in the retrospective studies indicated that there is high prevalence of wound infection within the study environment. Although, the number of samples from male patients with wound infections were much higher than those from female patients (308 males compared to 199 females), the differences in the proportions with infection in each gender class were much less (79.59% males and 75.38% females). There was negligible correlation ($r = 0.12$) between gender and contracting wound infection. A similar result was also reported in India, the slight difference in the number of males to females with wound

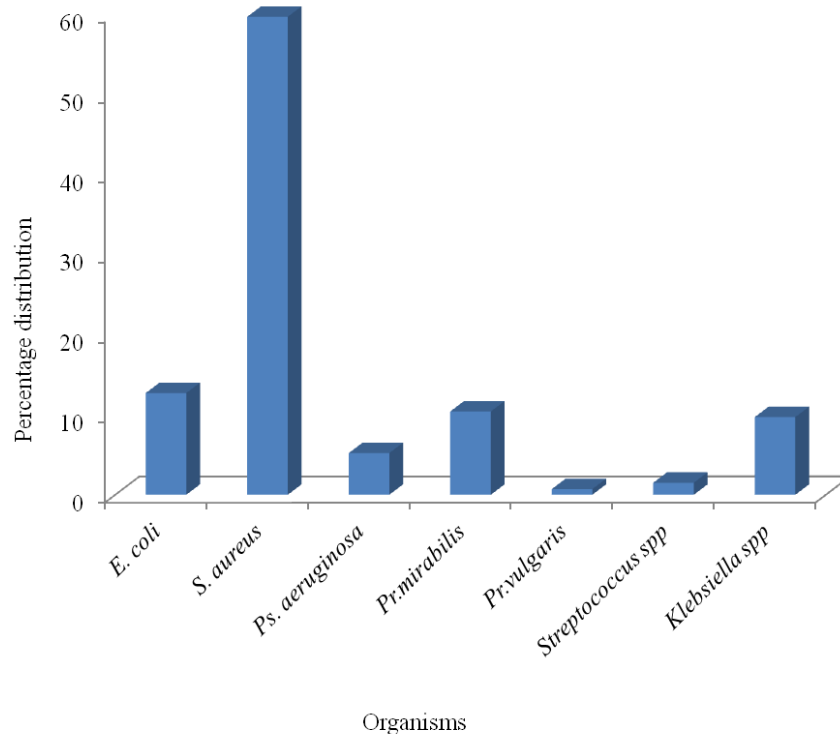


Figure 2. Percentage distribution of bacteria isolates from wound sepsis sites of patients attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010.

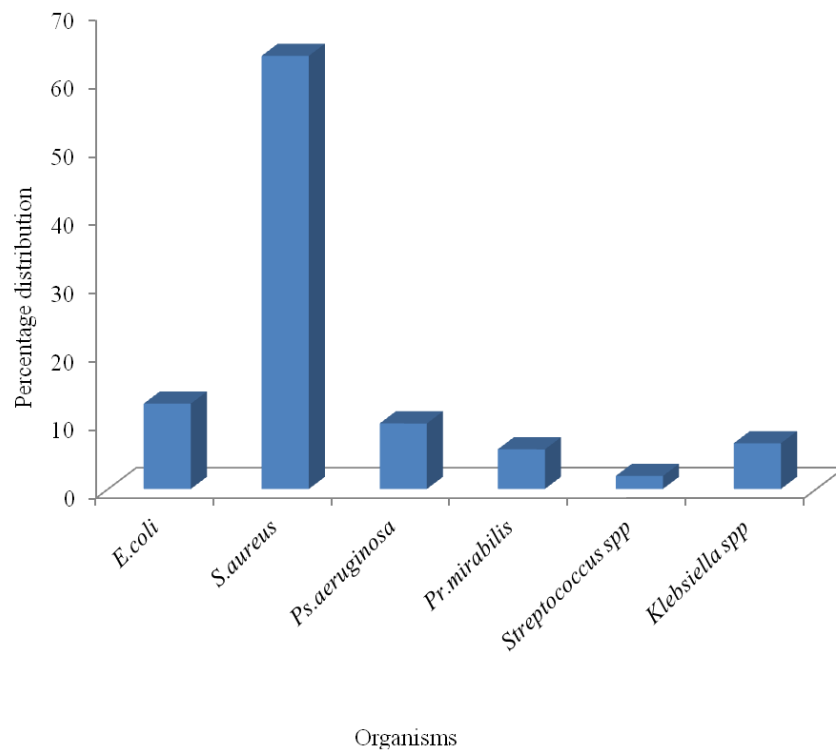


Figure 3. Percentage distribution of bacteria isolates from burn sites of patients attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010.

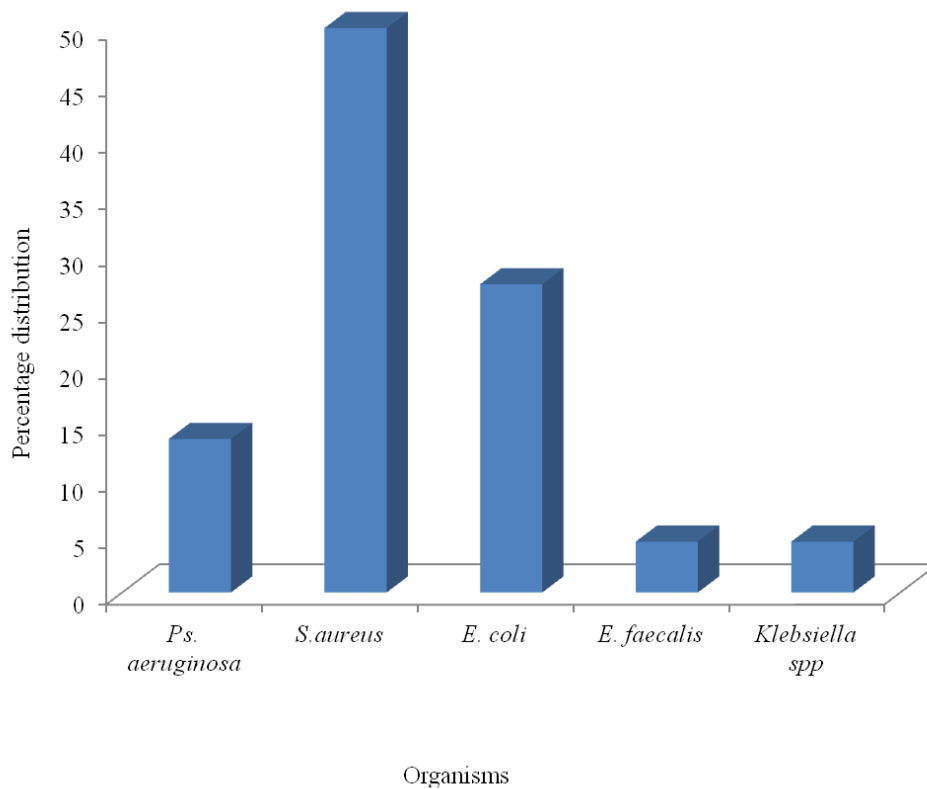


Figure 4. Percentage Distribution of Bacteria Isolates from Ulcer Sites of Patients Attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010

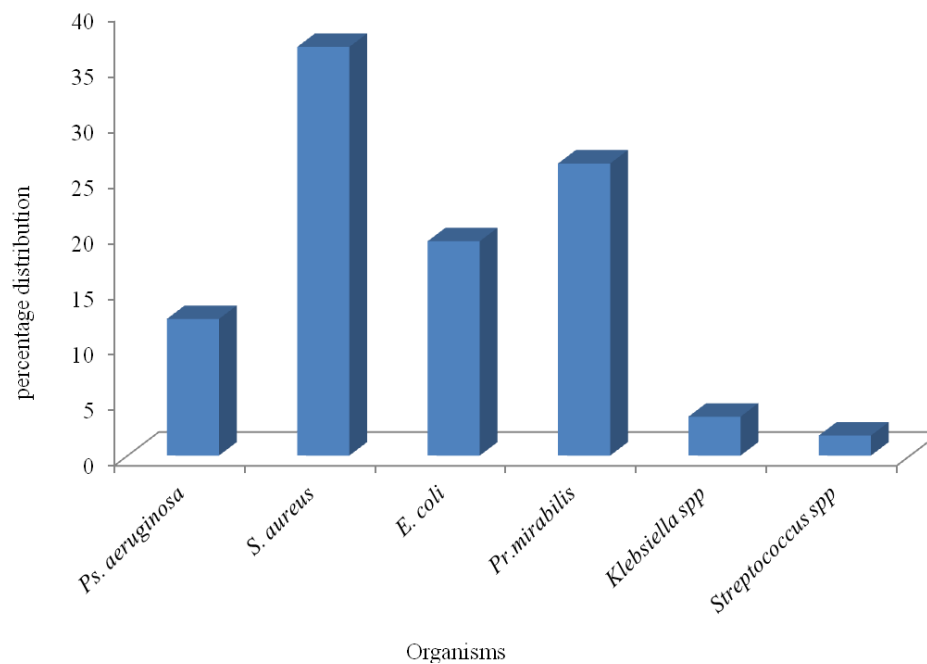


Figure 5. Percentage distribution of bacteria isolates from diabetic ulcer sites of patients attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010.

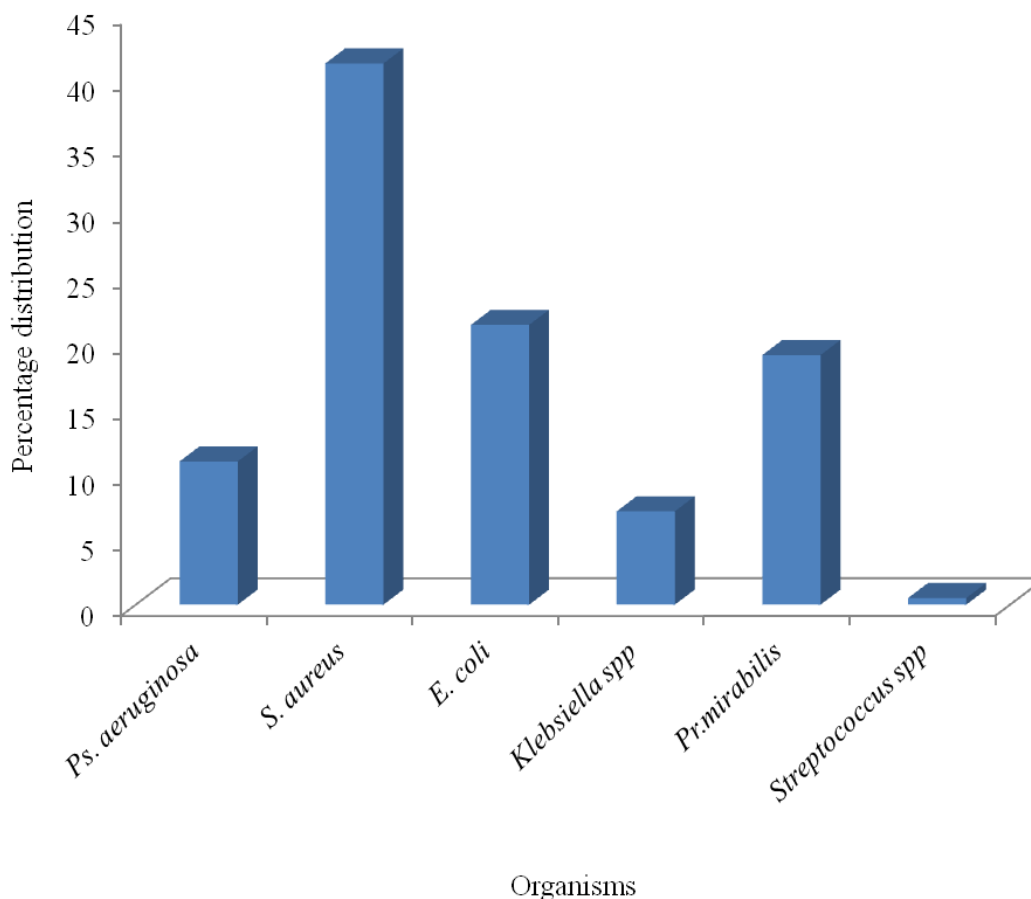


Figure 6. Percentage distribution of Bacteria Isolates from surgical wound sites of patients attending Aminu Kano Teaching Hospital from April, 2009 to September, 2010.

Table 2. Percentage distribution of antibiotic prescription pattern on wound infections in Aminu Kano Teaching Hospital.

Bacteria isolates	Pen	Ceph	Aminog	Quinol	Mac	Tet	Sulph
<i>E. coli</i> (n = 92)	36.9	25.4	21.9	13.7	2.1	0	0
<i>Ps. aeruginosa</i> (n = 49)	16.2	57.3	16.2	10.3	0	0	0
<i>S. aureus</i> (n = 267)	38.2	21.2	20.0	17.2	2.8	0.2	0.4
<i>Pr. mirabilis</i> (n = 7)	30.4	21.5	20.7	24.5	2.9	0	0
<i>Pr. vulgaris</i> (n = 1)	100	0	0	0	0	0	0
<i>E. faecalis</i> (n = 1)	100	0	0	0	0	0	0
<i>Streptococcus spp</i> (n = 6)	36.4	27.1	27.4	9.1	0	0	0
<i>Klebsiella spp</i> (n = 37)	29.1	28.9	23.7	18.3	0	0	0

Pen = penicillins, Ceph = cephalosporins, Aminog = aminoglycosides, Quinol = quinolones, Mac = macrolides, Tet = tetracyclines, Sulph = sulphonamides.

infection is due to the social behavior where males are given superiority to the females, and if contacted disease are brought immediately to hospitals in comparison to female for treatment (Aizza et al., 2007). The proportion

of adults with wound infection was much higher than children, and there was a moderate correlation ($r = 0.43$) between age and contracting wound infection. This could be due to the fact that more adults are likely to undergo a

surgical operation which is the site that is mostly infected.

It is not surprising that the three microorganisms most frequently isolated from the wound samples in the retrospective study were *S. aureus*, *E. coli* and *Ps. aeruginosa*. The frequent occurrence of *S. aureus* and the Gram negative organisms has also been reported (Olayinka et al., 2004; Sani et al., 2012). The preponderance of *S. aureus* (58%) in the retrospective data is in conformity with findings from other studies (Taiwo et al., 2002).

It was observed that Surgical site infection ranked highest among wound infections. This report is in agreement with the result of Taiwo et al. (2002). This is attributable to the fact that patients are likely to undergo surgical operations and more likely to have breaks in their local defence system. Wound sepsis which includes acute soft tissue infections follows surgical site infection in prevalence. Similar findings have also been reported (Aizza et al., 2007). In wound sepsis, *S. aureus* was also the most prevalent infectious organism caused by incision or fluid collection under the skin surface. This finding is similar to that obtained by Akinjogunla et al. (2009). The susceptibility of burn wound to opportunistic colonization by bacteria and fungi results from several factors, including the presence of coagulated proteins, the absence of blood-borne immune factors, and the avascularity of the burn wound (Jefferson and João, 2005).

Further analysis of the retrospective studies also showed that *S. aureus*, *Ps. aeruginosa*, *E. coli* and *Pr. mirabilis* are associated with surgical site infections. This finding is similar to that reported by (Nwachukwu et al., 2009) who found that 41.2, 21.3, 19 and 10.9% were *S. aureus*, *E. coli*, *Pr. mirabilis* and *Ps. aeruginosa*, respectively. The relatively high number of Enterobacteriaceae isolated in this study points to the fact that the presence of enteric organisms in the wounds at operation probably resulted to subsequent sepsis. This finding, therefore, infers that enteric organisms are important determinants of healing in surgical wounds. The incidence of the enteric bacteria also confirms the observation that most wound infections arising from abdominal procedures are presently acquired from the patient's own faecal flora (Jonathan et al., 2008).

Although, several antibiotics were in use, based largely on the organisms isolated from the wound sites; it has been suggested that treatment should be based on the patient as a whole and not the infection alone, and that management strategies must be based on data derived from a holistic assessment of the needs of the individual (Collier, 2003).

Conclusion

Bacteria isolates associated with wound infections in the retrospective study, which were mostly *S. aureus*, enteric bacteria and *Ps. aeruginosa* are consistent with reports of similar studies conducted globally and in various parts of the country. The most commonly prescribed antibiotics in the facility were the penicillins, cephalosporins, aminoglycosides and quinolones. The correct choice of antibiotics should be made only after antibiotic sensitivity testing.

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Full Length Research Paper

Application of area to point Kriging to breast cancer incidence in Ashanti Region of Ghana

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This paper provides a spatial analysis of breast cancer incidence in the Ashanti region area during the period of 2010 to 2011. Breast cancer disease has prevalence in Ghana particularly in the major cities including Ashanti region. Geographical units vary in shape and size and incidence count is non homogeneous in nature. For this reason, assigned area to point kriging approach is adopted as methodology. There is a large range of spatial autocorrelation in ages above 40 years than that of below 40 years in the various administrative units. The surrounding administrative units in the regional capital are less endemic for women whose ages are above 40 years. However, for those whose ages are below 40 years in all the surrounding administrative units are endemic but the capital is not. Most of the endemic districts share boundaries with Kumasi metropolis, the regional capital, where the only Teaching hospital is located. Most of the districts do not have good health facilities where women report for early treatment.

Key words: Area to point kriging, breast cancer, area to area, kriging.

INTRODUCTION

The leading malignancy in Ghana is breast cancer (Archampong, 1977). This is responsible for 15.4% of all malignancies and seems to be on the increase (Archampong, 1977). In 2011 there has been rise in admission for malignant neoplasms at the Komfo Anokye Teaching hospital of which most of the cases were breast cancers. Ghana has seen tremendous public education about breast cancer within the last few years and some of the non-governmental organizations such as Mammocare Ghana, Cancer Society of Ghana and others have been playing pivotal role in dissemination of information about this disease. More than fifty percent of Ghanaian women have reported the issue of breast cancer at the hospitals when the disease may be at its advanced stage (Badoe

and Baako 2000). In terms of average most of these women report eight months or more after observing a change in their breast (Biritwum et al., 2000). These patients are referred to the Komfo Anokye Teaching hospital where they go for treatment at the surgical outpatient's clinic.

Breast cancer disease incidence rate recorded at districts level are areal data which is good for areal data mapping in geostatistics. This has been implemented by several authors including Goovaerts and Jacquez (2005) and Kyriakidis (2004) to predict areal values. This approach is referred to as "area-to-point" (ATP) or "area to area" (ATA) kriging as following Kyriakidis (2004). The unique feature about ATP kriging is that it allows the mapping of variability within geographical unit (polygon) and at the same time ensuring the coherence of the prediction. For instance, disaggregated estimates of count data are non-negative and the sum is equal to the

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original aggregated count.

Kerry et al. (2010a) applied ATP and ATA for analyzing the geography of offenses and for identifying significant clusters of crimes on car-related thefts in the Baltic states. Shao et al. (2009) applied ATP to introduce sex for the cancer rates, and observed the difference between age-adjusted rates and age-sex-adjusted rates.

Goovaerts (2006a) used this technique for cancer data analysis. This approach applied areal supports to predict point values by taking into account the spatial support of data as well as the varying population size. ATP and ATA are capable of analyzing cancer count and mortality maps making it possible to incorporate the shape and size of administrative units into the smoothing of choropleth maps and the creation of isopleths risk maps, respectively.

This paper presents a geostatistical analysis of breast cancer incidence data that consists of three steps: (1) filtering of noise in the data using Poisson kriging where the shape and size of administrative units is incorporated into the filtering, (2) the mapping of the corresponding risk at a fine scale and (3) geographical clustering of the disease at the administrative units.

METHODOLOGY

Study area

The Ashanti Region is centrally located in the middle belt of Ghana. It lies between longitudes 0.15° W and 2.25° W, and latitudes 5.50° N and 7.46° N. The region shares boundaries with four of the ten political regions, Brong-Ahafo in the north, Eastern Region in the east, Central Region in the south and Western Region in the South west. The region occupies a total land area of 24,389 km² representing 10.2% of the total land area of the country.

It is the third largest region after Northern (70,384 km²) and Brong Ahafo (39,557 km²) regions. The region has a population density of 194 persons per square kilometer, the third after Greater Accra and Central Regions.

The total population of the region is 4,725,046 made up of 2,288,325 males and 2,436,721 females (Ghana Statistical Service, 2010). The average daily temperature is about 27°C. Much of the region is situated between 150 and 300 m above sea level. The region has one Teaching hospital situated at the regional capital Kumasi and serves the entire region and beyond for tertiary cases. The rest of the 26 administrative units mostly do not have district hospitals and where they exist there are not enough qualified personnel to manage these facilities.

Data sources

The Ashanti region has a Disease Control Units (DCU) to which all District Health Directorates (DHD) report confirmed cases of various diseases at the end of year. In addition to this, the Teaching Hospital within the region has a research unit where various database of diseases are kept. Some of the confirmed cases of cancer disease were obtained from this centre and compared to that of the various District Disease Control Units.

Data for the analysis were classified based on ages below and above 40 years within each administrative unit. This was to find out the incidence rates difference between the two groups of women.

Population data obtained from Ghana Statistical Service was

used in computing the raw rates of cancer. Raw rates were calculated as the number of cancer cases in each district divided by the estimated Population in 2010. In order to put the risk better, the raw rates were rescaled by multiplying it by a factor of 100,000. This expresses the raw rates as per 100,000 people

Spatial and non-spatial data input

The basic data inputs were topographic map data, geographic location of the study area where breast cancer cases with patients ages been reported. Topographic map of Ashanti region at a scale of 1:25000 was obtained from Accra Survey and Mapping unit (Figure 1). This was georeferenced and digitized in ArcGIS version 10.0 where coordinates per polygon were extracted from the map.

Reported cases of breast cancer and ages of patients with confirmed breast cancer cases obtained from Komfo Anokye Teaching Hospital (KATH) and Disease Control Units (DCU) were entered as attributes of the polygon features (that is, the District) in the software. Application software are ArcGIS version 10.0 developed by ESRIL and SpaceStat 3.6.1 developed by BioMedware USA.

Geostatistical analysis

Area to Area (ATA) Poisson kriging

Given number N of geographical units v_α (administrative units), represent the observed mortality rates Cancer areal data as $v_\alpha = d(v_\alpha) / n(v_\alpha)$, where $d(v_\alpha)$ is the number of Cancer counts and $n(v_\alpha)$ is the size of the population at risk. The Cancer incidence is explained as realization of a random variable $D(v_\alpha)$ that obeys a Poisson distribution with one parameter (expected number of count) simply the product of the population size $n(v_\alpha)$ by the local risk $R(v_\alpha)$.

The risk is computed as a linear combination of rate $z(v_\alpha)$ and the rates observed in $(K-1)$ neighbouring entities v_i :

$$\hat{r}(v_\alpha) = \sum_{i=0}^k \lambda_i z(v_i) \quad (1)$$

We compute weights λ_i assigned to the K rates by solving the number of system of linear equations known as "Poisson kriging" system:

$$\sum_{j=1}^K \lambda_j \left[\bar{C}_R(v_i, v_j) + \delta_{ij} \frac{m^*}{n(v_i)} \right] + \mu(v_\alpha) = \bar{C}_R(v_i, v_\alpha) \quad (2)$$

$$\sum_{j=1}^K \lambda_j = 1$$

Where δ_{ij} if $i=j$ and 0 otherwise and m^* is the population-weighted mean of the N rates. The "error variance", $m^*/n(v_i)$ help to locate

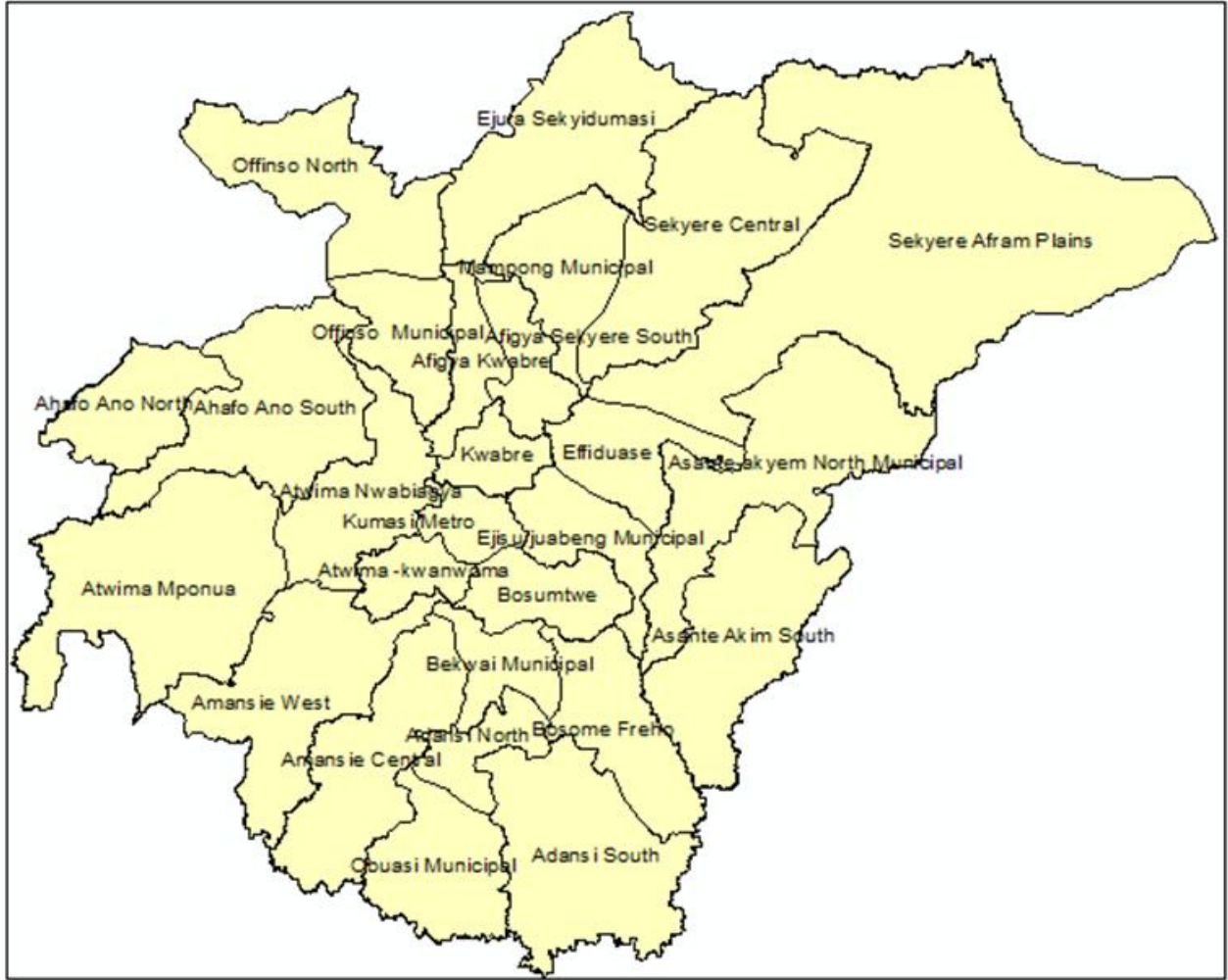


Figure 1. Map of Ashanti region of Ghana indicating District names.

small weights for less reliable data. The spatial correlation among geographical units through the area-to-area covariance terms $\bar{C}_R(v_i, v_j) = Cov\{Z(v_i), Z(v_j)\}$ and $\bar{C}_R(v_i, v_\alpha)$.

Covariance is then between any two locations discretizing the area v_i and v_j :

$$\bar{C}_R(v_i, v_j) = \frac{1}{\sum_{s=1}^{P_i} \sum_{s'=1}^{P_j} w_{SS'}} \sum_{s=1}^{P_i} \sum_{s'=1}^{P_j} w_{SS'} C(u_s, u_{s'}) \tag{3}$$

Where P_i and P_j are the number of points used to discretize the two areas v_i and v_j respectively. We compute the weights $w_{SS'}$ as the product of two population sizes assigned to each discretizing point u_s and $u_{s'}$:

$$w_{SS'} = n(u_s) \times n(u_{s'}) \quad \text{with} \quad \sum_{s=1}^{P_j} n(u_s) = n(v_j) \quad \text{and} \quad \sum_{s=1}^{P_i} n(u_{s'}) = n(v_i) \tag{4}$$

The uncertainty about the cancer mortality risk prevailing within the geographical unit v_α can be modeled using the conditional cumulative distribution function (ccdf) of the risk variable R , $Prob\{R(v_\alpha) \leq r|K\}$. Based on assumption of normality of the prediction errors, ccdf is modeled as a Gaussian distribution with the mean and variance corresponding to the Poisson kriging estimate and variance are computed as:

$$\sigma^2(v_\alpha) = \bar{C}_R(v_\alpha, v_\alpha) - \sum_{i=1}^K \lambda_i \bar{C}_R(v_\alpha, v_\alpha) \mu(v_\alpha) \tag{5}$$

Where $\bar{C}_R(v_\alpha, v_\alpha)$ is the within-area covariance that is calculated

according to Equation (3) with $v_i = v_j = v_\alpha$

Area- to- Point (ATP) Point kriging

The prediction support being small as point u_s resulting area-to-point Poisson kriging estimator and kriging variance:

$$\hat{r}_{PK}(u_s) = \sum_{i=1}^K \lambda_i(u_s) z(v_i) \tag{6}$$

$$\sigma^2_{PK}(u_s) = C_R(0) - \sum_{i=1}^K (u_s) \bar{C}_R(v_i, u_s) - \mu(u_s) \tag{7}$$

We compute the kriging weights and the Langrange parameter $\mu(u_s)$ by solving system similar to the ATA kriging system (2), apart from the right-hand -side term where the area-to-area covariance $\bar{C}_R(v_i, u_\alpha)$ are replaced by area-to-point point covariance $\bar{C}_R(v_i, u_s)$ that are simplified as:

$$\bar{C}_R(v_i, u_s) = \frac{1}{P_j} \sum_{s'=1}^{P_j} wss' C(u_s, u_s) \tag{8}$$

Where P_j and wss' are defined as in expression (3). ATP reduces visual bias and has coherence property. The population-weighted average of the risk values estimated at the P_α points μ_s discretizing a given entity v_α produces the ATA risk estimate for this entity:

$$\hat{r}_{PK}(v_\alpha) = \frac{1}{n(v_\alpha)} \sum_{s=1}^{P_\alpha} n(u_s) \hat{r}_{PK}(u_s) \tag{9}$$

Constraint (8) is fulfilled if the same K areal data used for the ATA $\hat{r}_{PK}(v_\alpha)$ are also used for the ATP kriging of the P_α risk values.

Deconvolution of the semivariogram of the risk

In ATA and ATP kriging we need knowledge of point support covariance of the risk $C(h)$ or similarly the semivariogram $\gamma(h)$. We cannot obtain this straightly since only the areal data is available. The regularized semivariogram of the risk can be estimated as:

$$\hat{r}_R(h) = \frac{1}{2 \sum_{\alpha, \beta} \frac{n(v_\alpha)n(v_\beta)}{n(v_\alpha) + n(v_\beta)}} \sum_{\alpha, \beta}^{N(h)} \left\{ \frac{n(v_\alpha)n(v_\beta)}{n(v_\alpha) + n(v_\beta)} [z(v_\alpha) - z(v_\beta)]^2 - m^* \right\} \tag{10}$$

where $N(h)$ is the number of pairs of administrative units (v_α, v_β) whose population-weighted centroids are separated by the vector h . The varying spatial increment $[z(v_\alpha) - z(v_\beta)]^2$ are weighted by a function of their respective population size $n(v_\alpha)n(v_\beta) / [n(v_\alpha) + n(v_\beta)]$, a term which is inversely proportional to their standard deviations (Monetiez et al., 2006).

Determination of a point-support semivariogram from the semivariogram $\gamma R(h)$ fitted to areal data is known as “deconvolution”, a common operation in geostatistics and it typically involves regular areas or blocks (Journel and Huijbregts, 1978). In this paper, we adopted the iterative procedure introduced for rate data measured over irregular geographical units in which one seeks the point-support model that, once regularized, is the closest to the model fitted to areal data; more details and simulation studies are found in Goovaerts (2006b).

Cluster analysis

A common task in disease analysis is to examine administrative units in adjacent geographical locations that are significantly similar or different. Similarity between the breast cancer incidence rate observed within area v_β and those recorded in the $j(v_\alpha)$ neighboring areas v_α can be computed by the local *Moran statistic* (Anselin et al., 2000) as:

$$I(v_\alpha) = \left[\frac{z(v_\alpha) - m}{s} \right] \times \left(\sum_{j=1}^{j(v_\alpha)} \frac{1}{j(v_\alpha)} \times \left[\frac{z(v_j) - m}{s} \right] \right) \tag{11}$$

where m and s are the mean and standard deviation of the set of N area incident rates respectively. This Local Indicator of Spatial Association (LISA) is simply the product of the kernel rate and the average of the neighboring rates.

The distribution of the local *Moran statistic* under the null hypothesis of complete spatial randomness is usually obtained through a random of shuffling all the count(s) except at v_α each time calculating (10) to get the distribution of simulated LISA values.

The empirical values of (10) are compared with this distribution to compute the P value for the rest. This randomization ignores the population size associated with each areal unit (Goovaerts and Jacquez, 2005).

RESULTS AND DISCUSSIONS

The Figures 2 and 3 show the omnidirectional variogram of breast cancer below and above 40 years risk computed from district-level rates using estimator (10). The experimental variogram was fitted using a Cubic model with a range of 13.4 km for breast cancer below 40 year and 32.52 km for above 40 years (Table 1).

However, breast cancer incidence above 40 years has better range of spatial autocorrelation than incidence below 40 years for each administrative unit. Each model was deconvoluted using the iterative procedure. In two

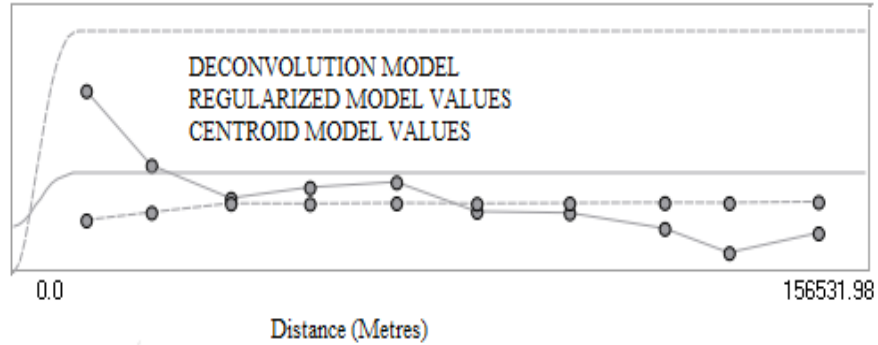


Figure 2. Experimental variogram and model from areal data; and theoretically regularized variogram and deconvoluted model for breast cancer below 40 years.

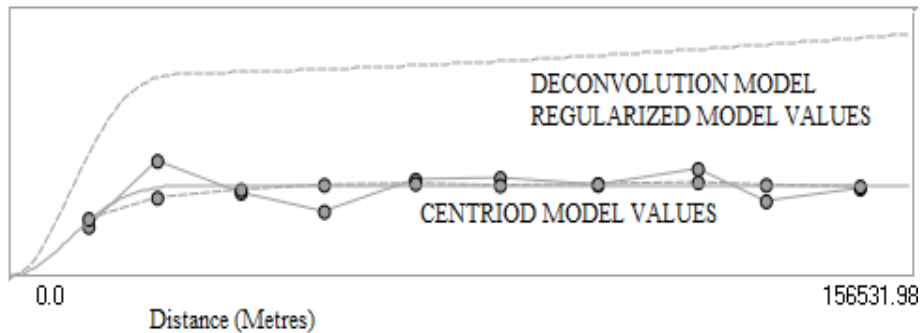


Figure 3. Experimental variogram and model from areal data; and theoretically regularized variogram and deconvoluted model for breast cancer above 40 years.

Table 1. Semivariogram parameters for both below and above 40 years breast cancer disease.

Name	Model type	Sill	Nugget	Range (m)	MSS Error
Breast Cancer Below 40 years	Cubic	0.1669	0	13435.76	2.667
Average Age Above 40 years	Cubic	0.237	0	32522.30	0.018

situations, the procedure ended once a small (that is, <2%) decrease in D statistic occurred four times, after 24 iterations for breast cancer 40 year and 13 for above 40 years.

The deconvoluted variogram model was used to estimate aggregated risk values at the district level in both region (ATA and ATP kriging) (Figure 4). In all cases, the estimation was based on K=32 closest observations which were selected according to the population- weighted district for ATA kriging. All maps are smoother than the map of raw rates since the noise due to small population sizes is filtered.

The breast cancer incidence rate below 40 years (Figure 4 A) indicates that the disease is more endemic around the regional capital Kumasi. The regional capital has the only teaching hospital in the northern sector of the country. There is similarity between the breast cancer

incidence rate and ATA (Figure 4 A and B).

This provides the isopleths map which does not reflect the viability at various administrative units. Almost all the administrative units surrounding the regional capital are more endemic and other areas (Figure 4 A and C) for ages below 40 years. The ATP provides the variability within each administrative unit also shows that all the administrative units surrounding Kumasi metropolis have high risk of cancer disease except Atwima Nwabiagya and Kwabre. These two places have seen good infrastructure development in terms of health facilities. There are other places such as Ofinso North and Asante Akim South which is also endemic and these areas are poorly developed in terms of infrastructure and human resource for them to manage the health facilities even if they exist. In Obuasi municipality there is variability of risk of breast cancer and there is a need to do further research to

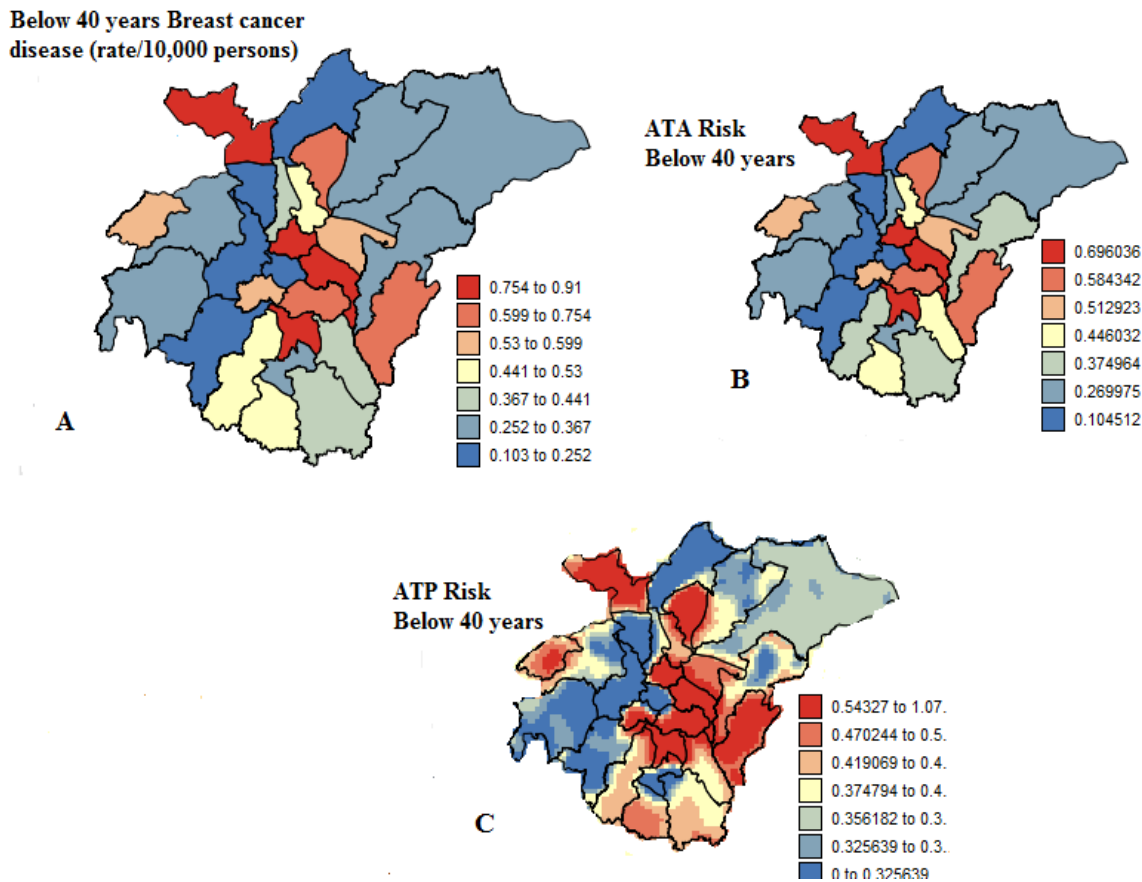


Figure 4. Maps of breast cancer incidence rate estimated by breast cancer rate per 10,000 person, ATA Poisson kriging and ATP kriging on ages below 40 years at various administrative units (A, B and C) respectively.

identify these specific places so that enough education could be conducted for early attendance to health facilities. There are some remote administrative units such as Amansie West, Sekyere Afram Plains and others have very low risk of breast cancer disease within the region.

The breast cancer incidence rate above 40 years for rate per 10,000 persons and ATA risk are similar (Figure 5 A and B). There are risk in most of the areas including Sekyere Afram Plain, Offinso North, Ahafo Ano North, Kwabre, Adansi North and Adansi South. Some of these administrative units do not have even health post for primary medical care. Therefore these women whose ages are above 40 do not report the disease to the health facilities for early treatment.

These women who are above 40 years within the various administrative units are mostly unemployed to get money for treatment. In ATP risk (Figure 5F) which explains the variability within each administrative unit indicates the regional capital Kumasi which is endemic but the surrounding administrative units are less endemic for women above 40 years. Notwithstanding, there are some that are far from the regional capital and endemic including Sekyere Afram Plains, Offinso North, Asante

Akim South and others. These places share boundaries with other regions such Brong Ahafo and Eastern region. The proximity to health facility may account for the low reporting of the disease and some resort to herbal and spiritual healing. Kumasi has a renowned breast cancer NGO known as Breast Care International. They have been organizing free breast cancer screen for women within and around Kumasi metropolis. In most cases special attention is given to women above 40 years who are known to be prone to the disease.

The Local Moran statistics (Figure 6) shows that only Ofinso North and the regional capital Kumasi are significant for women with ages below 40 years. However, it is only significant in Amansie West for women with ages above 40 years in Ashanti region (Figure 6H). This could be one of the reasons why there is a low awareness in most of the administrative units especially those that share boundaries with other region. The regional capital Kumasi which has the teaching hospital and well trained personnel for screening for breast cancer and frequent outreach programme for various suburbs of the cities has improved the awareness of this disease.

However, the majority of the administrative units are not significant (p -value > 0.05). This does not imply that

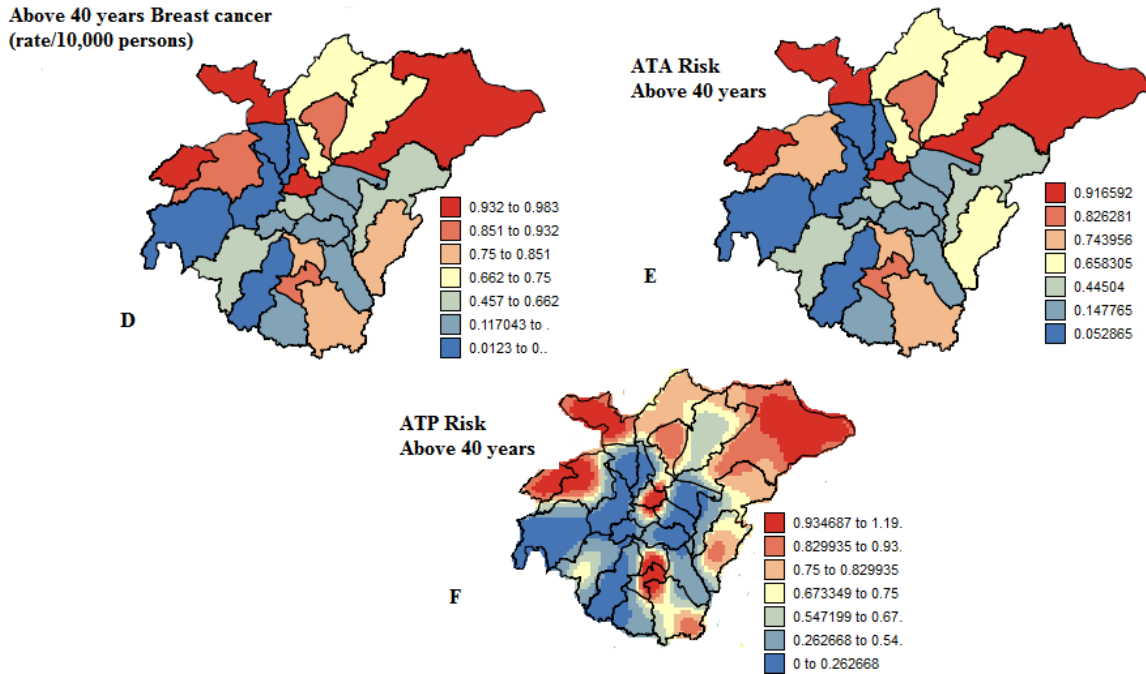


Figure 5. Maps of breast cancer incidence rate estimated by breast cancer rate per 10,000 person, ATA Poisson kriging and ATP kriging on ages above 40 years at various administrative units (D, E and F) respectively.

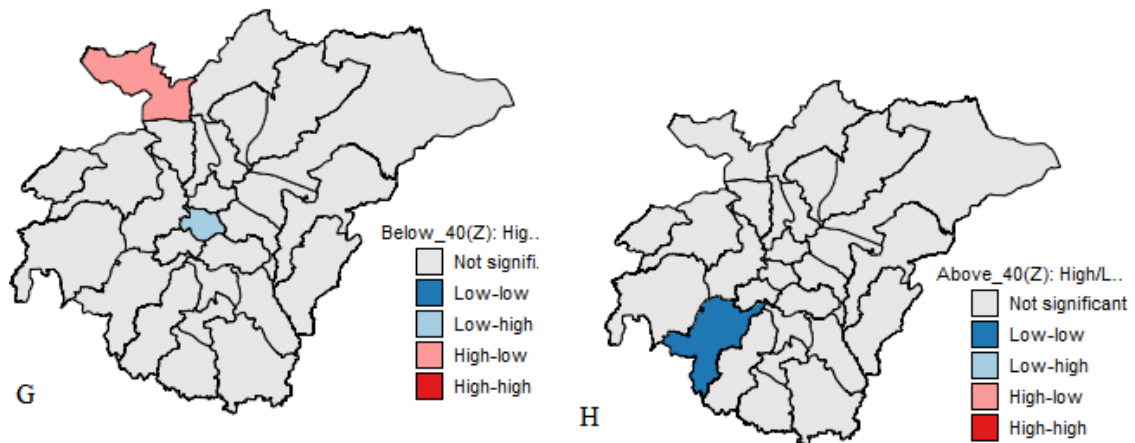


Figure 6. Results of the local cluster analysis conducted by breast cancer incidence rate for ages below and above 40 years (G and H).

these places are breast cancer free. The clustering of the disease in the central part for women with ages below 40 year (Figure 6G) is where we have the regional capital and is a densely populated area.

Conclusions

This study has demonstrated how the breast cancer incidence data can be analysed by considering average ages. ATP kriging is used to create a continuous risk

surface that reduces the visual bias associated with large administrative units. This approach of ATP kriging may also give insight into more localized potential “hot spots” that are not evident when areal count on rates are employed. There is large spatial dependency which exist in breast cancer data (Figures 1 and 2). The risk associated with breast cancer (Figures 3 and 4) is centered in the regional capital and administrative units that share boundary with Kumasi the regional capital. In both situations ages below and above 40 years the disease is endemic in administrative units that are far away from

Kumasi. The risk of people developing breast cancer in Ashanti is heterogeneous during the period 2010 to 2011.

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Full Length Research paper

Validation of pharmacokinetic model of propofol in Indian population

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The pharmacokinetics of propofol has been evaluated extensively in a variety of patients groups after either bolus doses or continuous infusions. Presently there are multiple models available based on western data including China. So far, the pharmacokinetics of propofol has not been studied in the Indian population. With this background we planned to evaluate pharmacokinetics of propofol in Indian patients which will help in better management of these patients undergoing surgery using propofol infusion in total intravenous anesthesia. Venous blood samples (3 ml) for estimation of propofol concentrations were taken at different time intervals. Plasma propofol concentration was estimated by using High Performance Liquid Chromatography (HPLC) method. Maximum performance error occurred at 2 min with a median of -3.85 and it varied from -1.7 to -9.5 showing a consistent over prediction of the concentration at two minutes after the loading dose and start of infusion. Subsequently the error decreased to median of -0.9 (-0.9 to 4.6) at 10 minutes and median of -0.3 (range -0.3 to 2.8) at 30 and in 60 min -1.55 (-0.28 to 1). When we compare the performance of our pharmacokinetic model of propofol in this study with other western studies, we observed less error with our pharmacokinetic model.

Key words: Propofol, pharmacokinetics, median performance error (MDPE), median absolute performance error (MDAPE).

INTRODUCTION

Propofol is an intravenous hypnotic agent which is widely used for induction and maintenance of general anesthesia. Its tremendous body uptake as well as the rapid elimination caused by huge volume of distribution and a high clearance makes propofol the best controllable intravenous anesthetic for maintenance of anesthesia at present. The pharmacokinetics of propofol has been evaluated extensively in a variety of disease states and different patients groups after either bolus doses or continuous infusions (Kay et al., 1986; Gepts et al., 1987; White and Kenny, 1990; Kirkpatrick et al., 1988; Cockshott et al., 1987). Presently there are multiple models available based on western data (Marsh et al., 1991). So far, the pharmacokinetics of propofol has not been studied in the Indian population. Previously we have

studied pharmacokinetics of propofol following single bolus dose of 2 mg/kg in healthy Indian adult patients followed by serial plasma propofol concentration estimation and found Pharmacokinetic model of Propofol (Puri et al., 2012). In this present study, we planned to validate the pharmacokinetic data by targeting specific plasma propofol concentration and maintaining target plasma concentration based on our model.

MATERIALS AND METHODS

After approval from the Institutional Ethics Committee and written informed consent, 10 ASA grade 1 20 to 40 years old Indian patients were included. All patients underwent surgeries requiring general anesthesia for less than two hours and expected blood loss less than 10% of total blood volume. Patients with previous adverse exposure to propofol and who received propofol bolus or infusion within 15 days were excluded from the study. Patients with hepatitis, HIV infection, hepatic, renal, hematological and cardiovascular diseases were excluded from the study. No pregnant

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patient and no patient with history of smoking or alcohol intake were included in the study.

Patients were premedicated with Tab Diazepam 5 mg night before as well as 2 h before induction. Before induction of anesthesia two large bore intravenous lines were secured. One in the antecubital vein and other in dorsum of the contralateral hand. The antecubital vein was used for blood sampling. Morphine 0.12 mg/kg was injected 5 min before starting propofol injection. Injection Lignocaine 2% 1 ml was injected in the iv line before injecting Propofol.

Propofol was administered as bolus dose followed by decreasing infusion rate calculated based on pharmacokinetics data of present pharmacokinetic model of propofol. The propofol infusion rate was delivered by syringe infusion pump (Pilot C Fresenius cabi) by using computer controlled. The propofol concentration was set at 3 µg/ml in 3 patients. 3.25 µg/ml in 3 patients and 3.5 µg/ml in 4 patients.

Blood sampling

Venous blood samples (3 ml) for estimation of propofol concentrations were taken at the following intervals after propofol injection and at 0 min (just before injection) and then at 2, 10, 30, and 60 min after administration of propofol bolus and infusion. Plasma propofol concentration was estimated by using HPLC method (Pavan and Buglione, 1992).

Infusion rate calculation

In the, present Propofol model, we found significant correlation in between volume of central compartment and weight of the patients and based on the equation,

$$Y=147.18x+4181.9$$

After the body weight and target concentration had been entered into the computer, loading dose was calculated based on target concentration and volume of central compartment using formula given below

$$LD = \text{Target concentration} \times \text{Volume of central compartment}$$

Immediately following bolus dose, in each patient, fixed plasma concentration of propofol (3, 3.25 and 3.5 µg/ml) were maintained till the end of the surgery using decreasing infusion rate.

$$R_1 = LD \times (K_{12} e^{-K_{21}t} + K_{13} e^{-K_{31}t} + K_{10})$$

R is the continuously decreasing infusion rate to match the distribution into the second and third compartment; LD is the loading dose;

K_{12} = rate constant from central to tissue compartment

K_{21} = rate constant from tissue to central compartment

K_{13} = rate constant from central to deep tissue compartment.

K_{31} = rate constant from deep tissue compartment to central compartment

K_{10} = Elimination constant

And t is the time in seconds following bolus.

Mean values of rate constant obtained from present pk model

$$K_{12}=0.13 \quad K_{21}=0.10 \quad K_{13}=0.05 \quad K_{31}=0.01 \quad K_{10}=0.08$$

Decreasing infusion rate was calculated using equation 'A' every 10 s and rate of infusion changed every 10 s by computer.

Validation of Model

Validation of model was assessed by measuring the plasma concentration at specific time intervals (2, 10, 30 and 60 min) calculating median performance error (MDPE), median absolute performance error (MDAPE), wobble, divergence (time related trends) using methods described by Varvel et al. (1991).

The predicted and measured values of propofol concentration were compared and various variables were derived as below.

Offset is the difference between predicted value and the measured value and it was calculated at each time point where measured concentrations were available that is, 2, 10, 30, and 60 min.

Offset = Measured concentration - Predicted concentration

The performance error was calculated by the formula

$$\text{Performance error (\%)} = \frac{C_p(\text{measured}) - C_p(\text{predicted})}{C_p(\text{predicted})} \times 100$$

Median Performance error (MDPE)

The percentage median performance error (MDPE) which reflects the bias in the *i*th subject is a signed value and represents the direction (over or underprediction) of the performance error.

$$MDPE_i = \text{median} \{PE_{ij} \mid j = 1, \dots, N_i\}$$

It is used to measure the systematic tendency of the system to underestimate or overestimate the measured concentration of blood propofol, that is, if bias has a positive value; it indicates that measured value is on an average greater than the system prediction and vice versa.

Median absolute performance error (MDAPE)

The percentage median absolute performance error (MDAPE) indicates the measure of inaccuracy in the *i*th subject.

$$MDAPE_i = \text{median} \{|PE_{ij}| \mid j = 1, \dots, N_i\}$$

Where N_i is the number of $|PE|$ values obtained for the *i*th subject.

Wobble

Wobble is another index of the time related changes in performance and measures the intrasubject variability in performance errors. In the *i*th subject the percentage wobble is calculated as follows:

$$\text{Wobble} = \text{median} \{|PE_{ij} - MDPE_i|, j = 1, \dots, N_i\}$$

RESULTS

The mean age of patients in this study was 28.4 ± 6.8 years and mean weight was 55.1 ± 9.2 Kg and the mean height was 154 ± 5.2 cm (Table 1).

Propofol concentration measured in plasma at different time points in all the patients followed the target concentration fairly well (Table 2).

Maximum performance error occurred at 2 min with a median of -3.85 and it varied from -1.7 to -9.5 showing a consistent over prediction of the concentration at two

Table 1. Demographic data of the patients

Parameter	mean \pm SD	Min.	Max.
Age (Years)	28.4 \pm 6.8	20	40
Weight (Kg)	55.1 \pm 9.2	40	67
Height (cm)	154 \pm 5.2	148	165

(Data expressed as mean \pm SD)**Table 2.** Showing predicted and measured concentration at different time intervals in different patients.

S/ no	T.C ug/ml	Rate(ml/h) at 2 min	MC at 2 in ug/ml	Rate(ml/hr) at 10 min	MC at 10 m in ug/ml	Rate(ml/h) at 30min	MC at 30 m in ug/ml	Rate(ml/h) at 60 min	MC at 60 m in ug/ml
1	3	42.6	2.89	31.3	2.97	22.3	3.09	19.5	3.03
2	3	50.1	2.88	36.8	2.85	26.3	3.04	22.9	2.95
3	3	56.3	2.89	41.9	3.14	29.5	3.01	25.8	2.99
4	3.25	48.2	3.02	35.4	3.22	25.3	3.18	22	3.2
5	3.25	58.3	3.09	42.9	3.17	30.6	3.22	27.2	3.15
6	3.25	60.4	2.94	44.4	3.11	31.6	3.22	28.2	3.02
7	3.5	69.4	3.37	51	3.35	36.4	3.46	31.7	3.52
8	3.5	67.9	3.3	49.9	3.52	35.6	3.4	31.1	3.42
9	3.5	54.1	3.41	39.8	3.54	28.4	3.6	24.7	3.49
10	3.5	60.7	3.29	44.6	3.44	31.8	3.51	27.7	3.53

TC--target concn, MC--Measured concn, Concentration in μ g/ml.**Table 3.** The performance error showing at various time points during the study in each patient.

S.No.	Name	Sex	Age (Yrs)	Weight (KG)	Height (cm)	Surgery	TC (ug/ml)	LD (ml)	Rate (ml/h) at 2 min	MC at 2 in ug/ml	Rate (ml/h) at 10min	MC at 10 m in ug/ml	Rate (ml/h) at 30 min	MC at 30 m in ug/ml	Rate (ml/h) at 60 min	MC at 60 m in ug/ml
1	PK	F	22	40	150	Tympanoplasty	3	3	42.6	2.89	31.3	2.97	22.3	3.09	19.5	3.03
2	Suj	M	26	52	160	Cleft rhinoplasty	3	3.5	50.1	2.88	36.8	2.85	26.3	3.04	22.9	2.95
3	SR	F	39	62	148	Hysterolap	3	3.9	56.3	2.89	41.9	3.14	29.5	3.01	25.8	2.99
4	Su	F	32	43	155	Hysterolap	3.25	3.4	48.2	3.02	35.4	3.22	25.3	3.18	22	3.2
5	San	M	24	58	165	MF amputation	3.25	4.1	58.3	3.09	42.9	3.17	30.6	3.22	27.2	3.15
6	Raj	F	28	61	155	Cystectomy	3.25	4.2	60.4	2.94	44.4	3.11	31.6	3.22	28.2	3.02
7	Bim	F	30	67	154	Hysterolap	3.5	4.9	69.4	3.37	51	3.35	36.4	3.46	31.7	3.52
8	Sat	M	20	65	155	NHU R Leg	3.5	4.8	67.9	3.3	49.9	3.52	35.6	3.4	31.1	3.42
9	San	F	23	48	148	PBC neck	3.5	3.8	54.1	3.41	39.8	3.54	28.4	3.6	24.7	3.49
10	Sha	F	40	55	155	Salphingophrectomy	3.5	4.2	60.7	3.29	44.6	3.44	31.8	3.51	27.7	3.53

Table 4. Analysis of MDPE, MDAPE, WOBBLE for 10 patients

S.no.	Patients	MEAN PE	MEAN OFFSET	MDPE*	MDAPE**	WOBBLE
1	PK	-0.16	-0.005	0	2	2
2	Suj	-2.3	-0.07	-2.8	2.8	1.6
3	SR	-2.9	-0.095	-1.8	1.8	0.61
4	Su	-2.8	-0.092	-2.7	2.7	1.87
5	San	-5.4	-0.177	-5.6	5.6	2.6
6	Raj	-2.1	-0.075	-2.4	2.4	1.5
7	Bim	-2.5	-0.09	-2.5	2.5	1.74
8	Sat	0.28	0.01	0.42	1.8	1.57
9	San	-1.6	-0.05	-0.7	1.28	1.28
10	Sha	0.25	0.0075	0	2	2
	MEAN	-1.923±1.7	-0.063±0.05	-1.8±1.8	2.4±1.18	1.67±0.5
	MEDIAN		-0.0725 (-0.005~ -0.17) [#]	-2.1(0~5.6) [#]	2.2(1.8~5.6) [#]	1.67(0.61~2.6) [#]

(MDPE)* Median Performance error. (MDAPE)** Median absolute performance error. [#]Data are expressed as medians (range)

Table 5. Comparison of performance errors of present study with Western data.

Comparison of performance of our study with western data				
VARIABLE	GROUP	MEDIAN	PERCENTILES	
			10%	90%
MDPE %	PRESENT STUDY	-2.1	-3.08	0.042
	Marsh et al. (1991)	-7	-42.6	42.7
	Dyck et al. (1991)	36.4	14.3	76.5
	Tackley et al. (1989)	-4.6	-35.6	24.6
	Hung et al. (2003)	14.9		
MDAPE %	PRESENT STUDY	2.488	1.748	3.08
	Marsh et al. (1991)	18.2	8.3	43.1
	Dyck et al. (1991)	39.3	15.4	76.5
	Tackley et al. (1989)	20.6	8.3	43.1
	Hung et al. (2003)	23.3		
DIVERGENCE %	PRESENT STUDY	0.2876	0.019	0.701
	Marsh et al. (1991)	6.5	-15.1	21.9
	Dyck et al. (1991)	14.6	-61.1	42.2
	Tackley et al. (1989)	6.9	-8.4	28.9
	Hung et al. (2003)	-1.9		
WOBBLE %	PRESENT STUDY	1.67	1.2	2.06
	Marsh et al. (1991)	10	4.5	29.6
	Dyck et al. (1991)	12	7.7	21.9
	Tackley et al. (1989)	14	7.5	21.6
	Hung et al. (2003)	18.9		

minutes after the loading dose and start of infusion (Table 3 and Figure 1). Subsequently the error decreased to median of -0.9 (-0.9 to 4.6) at 10 min and median of -0.3 (range -0.3 to 2.8) at 30 and in 60 min -1.55 (-0.28 to 1).

Table 4 shows the analysis of MDPE, MDAPE, WOBBLE for 10 patients. The Median prediction error (MDPE%) was found to be -2.1. The Median absolute

performance error (MDAPE%) was 2.2. The wobble calculated was 1.67.

Table 5 shows the comparison of performance errors of present study with Western data. In comparison to earlier studies of Marsh et al. (1991), Dyck et al. (1991), Tackley et al. (1989) and Hung et al. (2003) evaluating various pk models of propofol (Table 5) validation of present model

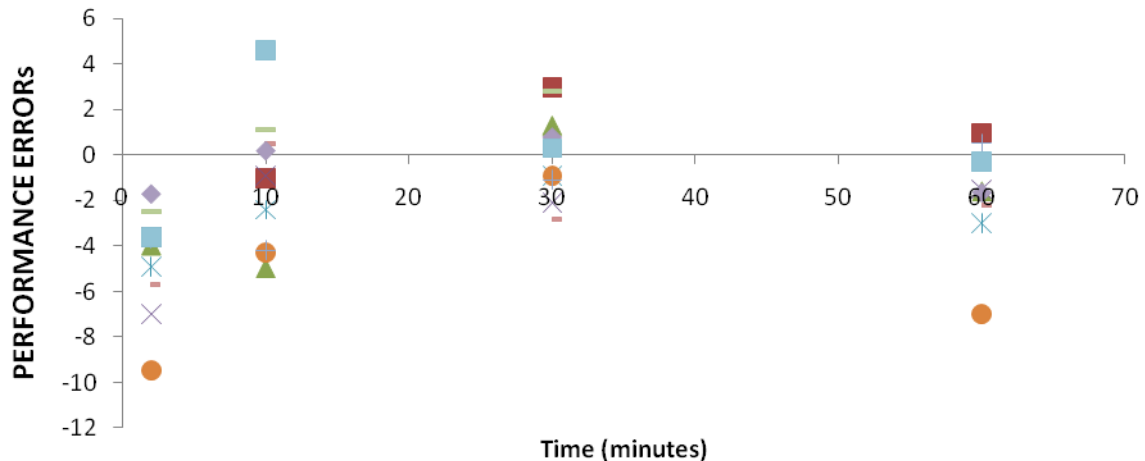


Figure 1. Showing performance error for measured concentration at various time stages.

showed better performance. The evaluation of Marsh model had to some extent comparable MDPE of -7% and MDAPE of 18.2%. Other studies like Dyck et al. (1991) showed much higher MDPE (36.45%) and MDAPE (39.3%). Similarly Tackley et al. (1989) showed MDPE % of -4.6% and MDAPE of 20.6. Hung et al. (2003) model showed 14.9% MDPE and MDAPE of 23.3% as compared to MDPE -2.1% and MDAPE 2.488% in our study. In our model the Median prediction error (MDPE%) was found to be -2.1 and percentiles showed that 10% values were lower than -3.08 and 90% values were lower than -0.042. The Median absolute performance error (MDAPE %) observed was 2.488 and percentiles showed that 10% values were lower than 1.748 and 90% values were lower than 3.08. The wobble calculated was 1.67 and percentiles showed that 10% values were lower than 1.2 and 90% values were lower than 2.06. When performance error of our model was evaluated with western model (Marsh et al., 1991; Dyck et al., 1991; Tackley et al., 1989; Hung et al., 2003), percentile calculation showed 10 and 90 percentile values in our study and was lower than those of western models. Thus our model showed less error compared to western models.

DISCUSSION

When we compare the performance of our pharmacokinetic model of propofol in this study with other western studies, we observed less error with our pharmacokinetic model. Though we did not evaluate other western model in our population but we compared the performance of our model obtained in present study with the performance of other models evaluated by Coetzee et al. (1995) in their respective studies. As obvious from the Table 4 we observed less error with our pharmacokinetic model. It has been suggested that the performance of a TCI system is clinically acceptable if the bias (MDPE) is no

greater than 10 to 20% (Glass et al., 1990). Performance bias may be minimized by using pharmacokinetic model derived from local population and including co-variables such as, weight etc to improve the performance of such model, that is, adjusting the pharmacokinetic model to individual patient optimize the precision of TCI. The precision (MDAPE) in Marsh model was 18.3% while in our study was 2.4%. Another reason for better performance in present study may be that we kept stable propofol concentration in each patient. Variation of plasma concentration with in patients during the study may have produce different performance results. Thus in our pharmacokinetic model derived from the pharmacokinetic data from Indian population is more acceptable as the performance error calculated were less compared to the western models.

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Full Length Research Paper

Sex differences in the cranial and orbital indices for a black Kenyan population

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Craniometric parameters including cranial and orbital indices have been employed to determine the sex of a person in forensic medicine. These parameters are usually population specific. However, they have not been documented for a black Kenyan population. This study aimed at calculating the sex differences in the cranial and orbital indices. The cranial vault height, glabellomaximal length and orbital height and length were measured from 150 crania (80 male and 70 female) using a sliding vernier caliper. Cranial and orbital indices were calculated and the results were analyzed. The cranial index was 71.04 for the male and 72.37 for the female ($P=0.095$). The orbital index was 82.57 and 83.48 for the male and female, respectively ($P=0.472$). From these results, although the cranial and orbital indices are within range of previously reported values for an African population, they cannot be used independently in sexing of black Kenyan crania.

Key words: Forensic, index, morphometric, sex determination.

INTRODUCTION

Sex determination from the skeleton can be assessed with reliability when the methods employed take into account a common sexual dimorphism between populations (Williams et al., 1995; Schimmilt and Cunha, 2006). Although, absolute sex differences seldom exist, there are some distinct differences observed in the cranial features of the male and female crania for given a population. Such dissimilarities are also known to occur between various geographical and ethnic groups. This is because the growth of the human skeleton is under the influence of several factors; among them are hormones, nutritional status, cultural differences and environmental factors (Chimmalgi et al., 2007). These morphometric sexual dimorphisms observed in the human crania have traditionally been used in sex determination involving forensic osteology (Parsons and Keene, 1919; Tripathi and Webb, 2007; Jacobs and Fishber, 2002). This has been either by visual techniques based on the evaluation of morphological traits or by statistical tools with bone measurements (Bruzek, 2002). Visual methods, if reliable,

are difficult to apply for new applicants and hence the use of metrical methods is preferred. Metric analysis to determine sex involves more than one measurement of the particular bone involved. The method used should employ a limited number of traits since increasing the number of variables does not provide a higher accuracy but rather makes the process time consuming and produces redundant results (Bruzek, 2002).

Different craniometric parameters have been employed to accurately and reliably determine the sex of a person in forensic medicine. These are either ratios of particular cranial lengths or areas of certain parts of the cranium (Parsons and Keene, 1919). Using metric lengths, various indices have been calculated. The ratio of the cranial vault breadth to the glabellomaximal length multiplied by 100 gives the cranial index (CI) (Golalipour, 2006). This index has been known to be higher in females than in males and shows interethnic variability (Parsons and Keene, 1919; Jacobs and Fishber, 2002). The CI is influenced by the shape of the head and hence the facial symmetry. It makes the orbits in dolicephalic individuals tend to look more laterally than in brachycephalic individuals (Patnaik et al., 2001).

The orbital index (OI), the proportion of the orbit height

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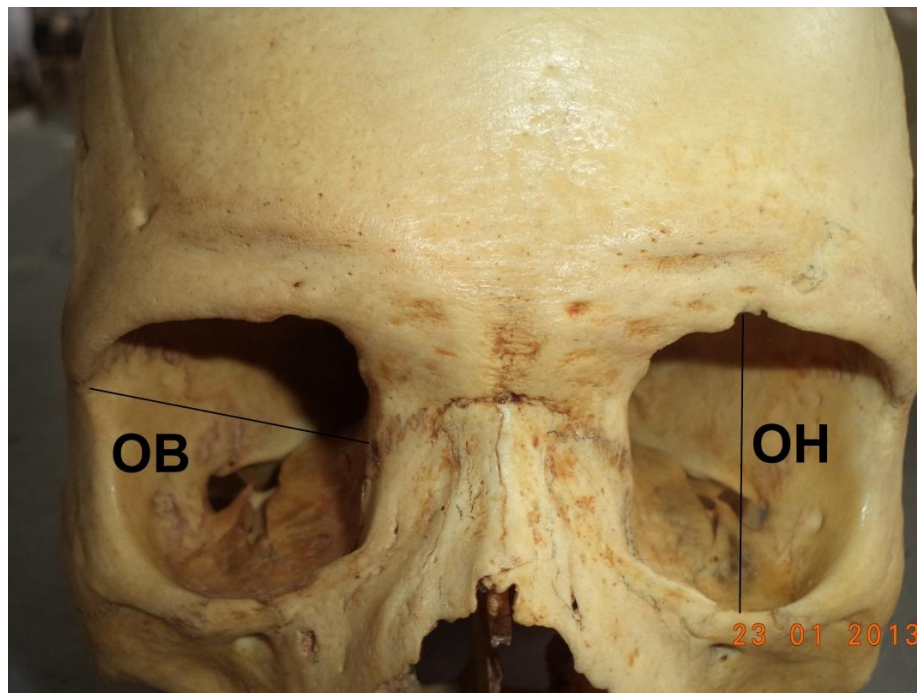


Figure 1. Diagram showing the orbital height, and orbital breadth. OB: Orbital breadth; OH: orbital height.

to its breadth multiplied by 100 (Igbigi and Ebite, 2010), is determined by the shape of the face and varies with race, regions within the same race and periods in evolution (Miyamoto, 1924; Black, 1928; Harrower, 1928; Shima, 1933). Among the blacks, it is usually higher in females than in males (Miyamoto, 1924).

From literature, the cranial and orbital indices of various communities have been documented and the sex differences have been noted. However, this has not been done for the black Kenyan population. Various natural and accidental circumstances may necessitate the use of anthropometry to identify the sex of a person. These include wars, road and train accidents and deliberate mutilation, disfigurement, pounding, or gauging of the body (Krogman and Iscan, 1986). Documentation of the ranges of these craniometric measurements would assist in skull identification and classification. Therefore, this study was done to compare sex differences in the two indices.

MATERIALS AND METHODS

Adult crania (age ranges between 22 and 67 years) of known sex were obtained from the archives of the Osteology Department, National Museum of Kenya, Nairobi. The bones represent the Central Kenyan ethnic communities and were from casualties of the pre-independence Mau Mau uprising of 1952 to 1963. The sex of the skeletons had been identified from records of slain citizens by the then authorities before being archived. Measurements from 80 male crania and 70 female crania were taken and analyzed. Non-sexed crania and those which had gross defects were excluded from the study. Measurements were taken using a sliding vernier

caliper (Franchois™ 2000) with an accuracy of 0.01 cm. Measurements for all crania were taken by the same person twice but at different sittings. Their average was then used in data analysis.

Each cranium was placed on a flat surface and the measurements were taken from a particular landmark. The following measurements were taken: glabellomaximal length, maximum cranial breadth, orbital height and orbital breadth.

The glabella is the most anterior part of the cranium, while the opisthocranium is the instrumentally determined most posterior part of the cranium. The opisthocranium does not lie on the external occipital protuberance (Kelly et al., 1999). These two points were used as the landmarks for the glabellomaximal length. The maximum cranial breadth was taken to be the maximum width of the skull perpendicular to the midsagittal plane, wherever it was located. This width excluded the inferior temporal lines and the area immediately surrounding them as these are inclined towards the midline in comparison to the superior temporal lines. The CI was calculated by dividing the maximum cranial breadth with the glabellomaximal length and multiplying the result by 100.

The ectochion, the intersection of the most anterior surface of the lateral border of the orbit and a line bisecting the orbit along its long axis, was used as a landmark for the most lateral point of the orbit. The sloping distance between the dacryon, the point on the medial border of the orbit at which the frontal, lacrimal, and maxilla bones intersect, and the ectochion was taken to be the orbital breadth (Figure 1). The orbital height was taken as the direct distance between the superior and inferior orbital margins perpendicular to the orbital breadth. The OI was calculated by dividing the orbital height with the orbital breadth and multiplying the result by 100.

All distances were expressed in millimeters and results were analyzed using Statistical Package for Social Sciences (SPSS) version 18. The means between the male and female samples were compared for significance using the Student t-test. The CI of each sex correlated with both the right and left orbital indices for that particular sex using the Pearson's correlation. Confidence interval

Table 1. Orbital index measures among adult Kenyans.

Side	Sex	Range	Mean
Right	Male (n=80)	72.62-92.63	82.72±5.01
	Female (n=70)	70.14-92.29	83.50±5.84
Left	Male (n=80)	72.40-92.38	82.42±3.50
	Female (n=70)	69.82-92.50	83.46±3.50

of 95% was assumed and the differences were considered significant at $P \leq 0.05$.

RESULTS

The CI was higher among the female subjects as compared to the males. Among the male subjects, the CI ranged between 58.06 and 78.49 (mean 71.04 ± 3.58). The female CI ranged between 60.60 and 81.13 (mean 72.37 ± 4.34). There was marginal statistically significant difference in the means of cranial indices of the male and female values (P -value 0.095). Of the total population studied, only 9% of the male population had a $CI > 75$, while for the female it was 25%.

In the male subjects, the OI ranged between 72.40 and 92.63 (mean 82.57 ± 5.01). On the other hand, the female OI ranged between 69.82 and 92.50 (mean 83.48 ± 3.50) (Table 1). There were no statistically significant differences in the orbital indices for both the right and left orbits of the two sexes (P -values of 0.472 and 0.389 for the male and female orbital indices, respectively).

The CI positively correlated with the OI for the respective sex. The Pearson correlation coefficient was 0.498 for the right eye and 0.458 for the left eye ($P=0.002$ and 0.006, respectively) for the male. For the female, the coefficient was 0.162 for the right eye and 0.205 for the left eye ($P=0.354$ and 0.237, respectively).

DISCUSSION

Craniometric parameters including cranial and orbital indices have been employed to determine the sex of a person in forensic medicine. The prior knowledge of these measures is paramount to their successful application since they are different from one population to another.

The CI is an important feature that is influenced by the shape of the head. It determines how close or apart the orbits will appear to be (Krogman and Iscan, 1986). It usually shows racial and ethnic variations (Parsons and Keene, 1919; Jacobs and Fishber, 2002). The CI was below 75 for both sexes reaffirming previous reports on African crania being dolicephalic (Jacobs and Fishber, 2002; Golalipour, 2006). The difference in the CI between the sexes although statistically marginal, suggests an

actual sex difference in the crania of a black Kenyan population. It cannot however be used on its own to sex a cranium. That the CI was higher in females than in males indicates that they have a relatively shorter cranium in relation to the cranial breadth as compared to their male counterparts. The results of this study support prior findings in which the CI was found to be higher for the female crania than for the male crania (Parsons and Keene, 1919; Jacobs and Fishber, 2002). There are however other research works among the African population that have found that male subjects have a larger CI than the female subjects (Oladipo and Olotu, 2006; Oladipo et al., 2009). This points out the much variability seen in the CI of various populations and that a population specific trend cannot be generalized to apply for other communities. Thus, there is a need to consider the group specific parameters when dealing with the CI when determining sex in forensic medicine.

The work of Parsons and Keene (1919) showed that the difference between the female and male cranial indices ranged between 0.4 and 1.6. The difference between the female and male CI in our case was 1.33. This agrees with Parsons and Keene (1919) findings. In the Orhobos of West Africa, the difference was 0.59 (Oladipo and Olotu, 2006). Such a small difference was also observed among the Jews (Jacobs and Fishber, 2002). This further highlights the inter population differences in the CI among various populations and hence the need to compute community specific indices. Since all these studies were done among subjects of different races, this could explain the difference in the CI of male and females in various ethnic groups. This seemingly group specific difference should be determined first before establishing from which sex a given cranium might belong.

Using the OI, three classes of orbits are recognized: megaseme (OI > 89) for the Orientals except the Eskimos, mesoseme (OI range between 89 and 83) for the Caucasians and microseme (OI ≤ 83) characteristic of the Africans (Tripathi and Webb, 2007). The higher OI found among orbits of female subjects was similar to what has been reported in previous studies conducted among different populations (Igbigbi and Ebite, 2010). There is however no statistical significance to warrant the use of the OI in sexing the crania from a black Kenyan population.

When the CI was correlated to the orbital indices, there was a greater strength of correlation for the male parameters as compared to those of the females. This was despite the female sex having greater cranial and orbital indices relative to the male sex. This observation seems to point out that a male cranium will have both large cranial and orbital indices when compared with the female cranium. Even though this correlation between the cranial and orbital indices gives the strongest evidence of sex dimorphism, it cannot be surely used to sex a cranium. Further measurements and tests are therefore

required.

Conclusion

From the results of this study, although the cranial and orbital indices are within the range of previously documented values for an African population, they cannot be used independently in sexing of black Kenyan crania. A correlation of the two indices might however be useful. We recommend that future studies should consider more measurements and further correlational analysis.

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Full Length Research Paper

A retrospective study on the outcomes of tuberculosis treatment in Felege Hiwot Referral Hospital, Northwest Ethiopia

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In this study, we investigated the outcomes of tuberculosis treatment at Felege Hiwot Referral Hospital in northwest Ethiopia. According to the World Health Organization (WHO), treatment outcome is an important indicator for tuberculosis (TB) prevention and control programme. We analyzed the records of 756 tuberculosis patients registered for treatment in Felege Hiwot Referral Hospital from January, 2010 to 2012. From the total of 756 TB patients, 331 (43.8%) were pulmonary tuberculosis (PTB) and 425 (56.2%) were extrapulmonary tuberculosis (EPTB) cases. Among the study subjects, 191 (25%) were Human immunodeficiency virus (HIV) seropositive. Of all patients, treatment outcome was classified as successfully treated 193 (26%), defaulted in 19 (2.5%), died in 44 (5.8%), treatment failed in 4 (0.5%) and transferred out in 496 (68.6%) patients. The percentage of deaths and defaulters was higher in females than in males. Being an older age group ($p = 0.004$), a rural resident ($p = 0.000$) and EPTB patients ($p = 0.004$) were associated with a lower treatment success rate, which are serious public health concerns that need to be addressed urgently. Therefore, treatment plans that emphasize Directly observed treatments (DOTS) for at-risk patients have the greatest success in improving tuberculosis treatment outcome in the region. Urgent need for strengthening treatment outcome monitoring to ensure effective program implementation and case management system in the study area is strongly recommended.

Key words: Treatment outcomes, tuberculosis patients, northwest Ethiopia.

INTRODUCTION

Tuberculosis (TB) is one of the leading causes of death in the world. Globally, around 8.8 million people develop

tuberculosis and 1.45 million people die every year due to TB, of which 0.35 million deaths are associated with HIV-TB co-infection (WHO, 2011). An increased incidence of tuberculosis is found mostly in Africa and Asia, where the highest prevalence of co-infection with HIV and *M. tuberculosis* also occurs (Issar, 2003; WHO, 2005). The global burden of death and disease caused by TB is

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concentrated particularly in low-income countries. Sub-Saharan Africa, including Ethiopia, is the area of highest prevalence of TB infection and in 2008, a WHO report showed that Ethiopia ranks seventh among the world's 22 countries with a high tuberculosis burden (WHO, 2008). At present, TB (all cases) is ranked fourth among leading causes of hospital admission and second in causes of hospital death in Ethiopia (MOH, 2004). According to the 2011 WHO report, the prevalence and mortality rate of all forms of TB in Ethiopia was estimated to be 623 and 42 per 82,950 individuals, respectively (WHO, 2011).

The WHO has implemented the Standardized Directly Observed Treatment, Short Course (DOTS)/Stop TB Strategy to scale up TB prevention and control. The TB control program in Ethiopia introduced DOTS as a pilot programme in 1992 and at Felege Hiwot Referral Hospital in 2000. DOTS geographical coverage reached 100% in 2006. However, the case detection rate is still below 50% (WHO, 2010). In the country, the health facility coverage is 75% (MOH, 2008). Although the WHO recommends routine culture and drug susceptibility testing for *M. tuberculosis* in order to effectively and timely follow-up on treatment outcomes, many developing countries including Ethiopia, do not perform it. It has been shown that patients taking drugs directly under the observation of health care providers have a paramount importance in achieving a high treatment success rate of 96.5% (Chaulk and Kazandjian, 1998).

Studies from developing countries have also reported that DOTS was significantly associated with a higher treatment success rate than self-administered therapy, as well as a lower tuberculosis-related mortality rate (Sumartojo, 1993). Besides the association of DOTS with treatment success rate, DOTS also aims to significantly decrease the occurrence of primary and acquired drug resistance and relapse (Weis et al., 1994). Even though the objectives of TB treatment are curing the patient, preventing the spread of tuberculosis infection, and preventing the emergence of new drug resistant strains, these plans are not achieved in many regions of the world (WHO, 2003) due to several factors that affect treatment success. These include: the severity of disease, co-infection with HIV and/or other diseases, multidrug resistance, poverty, and also the support provided to the patient.

Recommendations on how to evaluate treatment outcomes using standardized categories have been issued by the WHO in 2008. These categories were defined to assess the risk of future relapse and drug resistance. In Ethiopia, where there is no strong surveillance system, possible recognition and amendment of system failures is impossible. Some DOTS experiences in Ethiopia have been reported (Ramos et al., 2008; Tessema et al., 2009; Yassin et al., 2003). However, the level of treatment outcomes and associated risk factors has not been assessed in Felege Hiwot Referral Hospital. This study is aimed at investigating the outcomes of tuberculosis treat-

ment in Felege Hiwot Referral Hospital, northwest Ethiopia.

MATERIALS AND METHODS

Study location

The study was conducted at Felege Hiwot Referral Hospital in Bahir Dar, which is the capital city of Amhara National Regional State, 565 km away from Addis Ababa. The hospital is a tertiary health care level hospital serving the population of Bahir Dar town and remote areas of northwest Ethiopia. The total population served by the hospital is about 12 million. In the hospital, DOTS clinic is operating under the National Tuberculosis and Leprosy Program (NTLCP) of Ethiopia, under which patients are diagnosed with tuberculosis by examination of morning sputum smears by Zeihel-Nielsen staining, for the presence of Acid fast bacilli (AFB), chest radiographs, and for EPTB, pathological investigations were used. Patients are referred to the DOTS clinic where they are registered and treated according to the National Tuberculosis and Leprosy Control Program (NTLCP) (MOH, 2008).

Study design and data collection

A two-year retrospective descriptive analysis to assess treatment outcomes and risk factors of 756 TB patients registered from January, 2010 to 2012 was carried out in Felege Hiwot Referral Hospital's DOTS clinic. All 756 TB patients registered at the DOTS clinic were followed up during their course of treatment to assess treatment outcome. Demographic data such as patient's age, sex, address, as well as the study subject's clinical data HIV serostatus, tuberculosis type, and treatment outcome were included in the registration form. Patients' treatment outcomes were evaluated in accordance with the NTLCP which is adopted from the WHO (MOH, 2008) and classified as: cured (finished treatment with negative bacteriology result at the end of the treatment), treatment completed (finished treatment but without bacteriology result at the end of their treatment), defaulted (patients who interrupted their treatment for two consecutive months or more after registration), treatment failure (remaining smear-positive at five months despite correct intake of medication), died (patients who died from any cause during the course of treatment), transferred out (patients whose treatment result is unknown due to transfer to another health facility), successfully treated (a patient who was cured or completed treatment), and unsuccessful treatment (patients whose treatments were interrupted, transferred out or failed on treatment). Patients were provided with free TB medications for a period of 6 to 8 months by the DOTS centre in the hospital. Patients were followed up regularly until completion of their treatment.

Statistical analysis

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) software package, Version 16. For categorical outcomes, we calculated relative risks from the proportions in each group and tested the differences using the Chi-square test or the Fisher exact test. A p-value less than or equal to 0.05 was considered significant.

Ethical permission

Institutional ethical permission was obtained from the Research and Publication Committee Ethical Review Board of the Bahir Dar

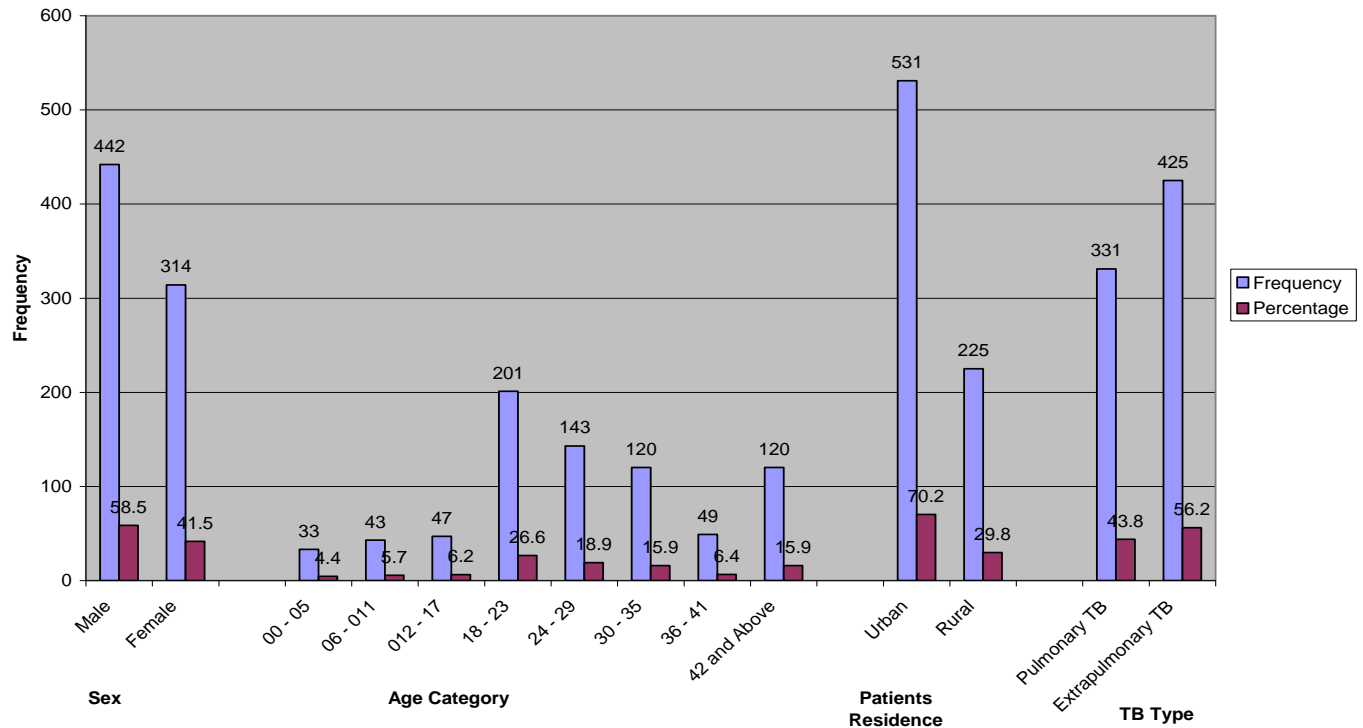


Figure 1. Distribution of TB patients (n = 756) by sex, age category, patients residence and TB type in Felege Hiwot Referral Hospital, Bahir Dar, North west Ethiopia 2010 to 2012.

University, Ethiopia

RESULTS

Demographic characteristics of study subjects

Out of 756 tuberculosis patients recorded at Felege Hiwot Referral Hospital between January, 2010 and 2012, 331 (43.8%) cases were PTB and 425 (56.2%) were EPTB patients. Of the total TB patients registered, 442 (58.5%) were males and 314 (41.5%) of them were females. The mean age of the patients was 29 years, ranging from 1.2 to 81 years. Four hundred and sixty four (61.4%) of the patients were in the age group 18 to 35 years. Figure 1 shows the general characteristics of the patients. Among the study subjects, 191 (25%) were HIV seropositive. Out of these, 94 (49.2%) were males and 97 (50.8%) were females. One hundred and fifty-five (81.1%) of the subset were from urban areas and the majority of them were also in the age group of 18 to 35 (Figure 2).

Treatment outcomes

The treatment outcomes of 756 tuberculosis patients are shown in Table 1. A successful treatment outcome (finished treatment with negative TB bacteria result at the

end of treatment and finished treatment, but without bacteriology result at the end of treatment) was achieved in 193 (26%) of the cases in the study. Meanwhile, only 19 treatment defaulters (2.5%), 44 deaths (5.8%), and 4 treatment failures (0.5%) were recorded. Four hundred and ninety-six (65.6%) patients were transferred out to other clinics in the same region. In this study, a higher death rate 3.3% (n = 25), failure rate 0.4% (n = 3), and defaulter rate 1.5% (n = 11) was recorded for female patients as compared to male patients. Table 2 shows the treatment outcome of seropositive tuberculosis patients by different characteristics.

Factors associated with TB treatment success

Patients with mean age greater than 29 had a significantly lower treatment success rate than other age groups who were being treated for TB, making a treatment success of 29.5% (RR = 1.6, 95% CI = 1.18 to 2.05, p = 0.004). Patients who were being treated for EPTB had lower treatment success than patients being treated for PTB (RR = 1.4, 95%CI = 1.13 to 1.84, p = 0.004). As expected, the study revealed that the risk associated with unsuccessful treatment outcome for people living in rural areas could be as much as seven times higher than for urban residents (RR = 7.0, 95% CI = 3.89 to 12.63, p = 0.000) (Table 3).

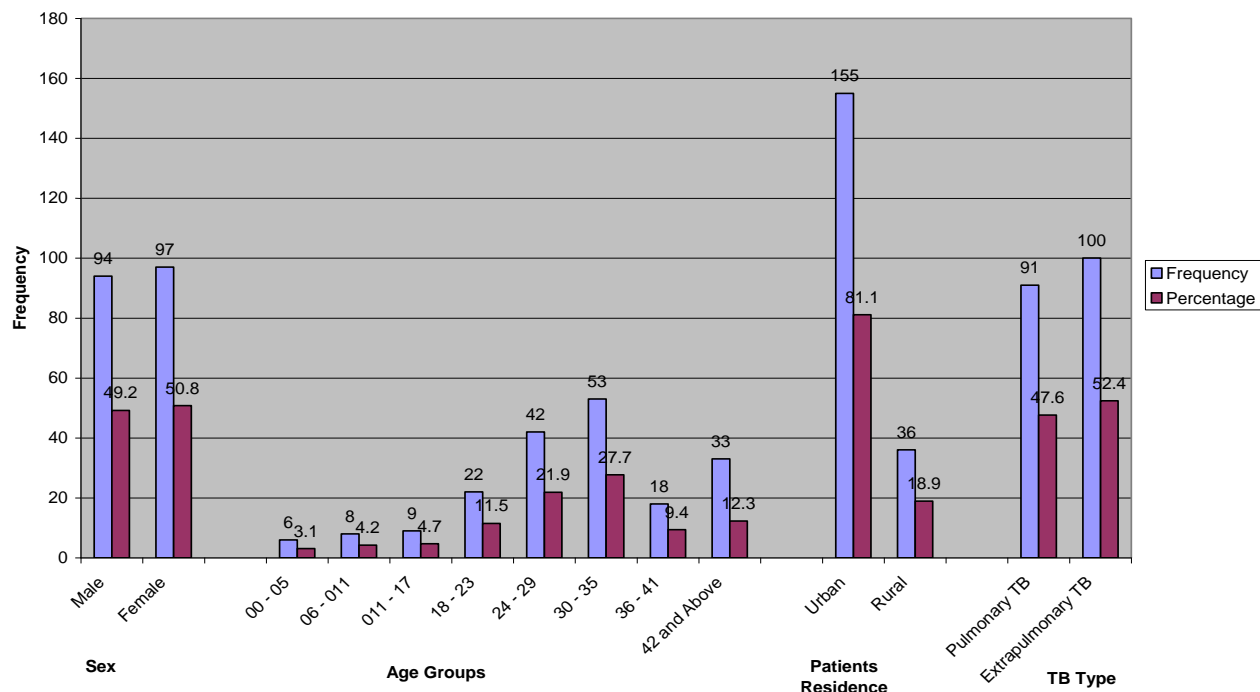


Figure 2. Seropositivity distribution of TB Patients (n = 191) by sex, age groups, patients residence and TB type in Felege Hiwot Referral Hospital, Bahir Dar, North west Ethiopia, 2010 to 2012.

Table 1. Treatment outcome of TB patients (n = 756) by sex, age group, residence, and tuberculosis type, Felege Hiwot Referral Hospital, Northwest Ethiopia, 2010 to 2012.

Characteristics	Treatment outcome						Total
	Cured N (%)	Rx completed N (%)	Died N (%)	Failure N (%)	Defaulted N (%)	Transferred out N (%)	
Sex							
Male	20(2.7)	99(13.1)	19(2.5)	1(0.1)	8(1.0)	295(39.0)	442
Female	13(1.7)	61(8.1)	25(3.3)	3(0.4)	11(1.5)	201(29.6)	314
Age (years)							
0-5	*	9(1.2)	*	1(0.1)	*	23(3.0)	33
6-11	*	6(0.8)	4(0.5)	2(0.3)	*	31(4.1)	43
12-17	1(0.1)	9(1.2)	1(0.1)	1(0.1)	1(0.1)	34(4.5)	47
18-23	20(2.6)	42(5.6)	3(0.4)	*	4(0.5)	132(17.5)	201
24-29	5(0.7)	46(6.0)	10(1.3)	*	2(0.3)	80(10.6)	143
30-35	4(0.5)	22(2.9)	15(2.0)	*	5(0.7)	74(9.8)	120
36-41	1(0.1)	9(1.2)	5(0.7)	*	*	34(4.5)	49
≥42	2(0.3)	17(2.2)	6(0.8)	*	7(0.9)	88(11.6)	120
Residence							
Urban	29(3.9)	153(20.3)	40(5.3)	*	8(1.0)	301(39.8)	531
Rural	4(0.5)	7(0.9)	4(0.5)	4(0.5)	11(1.5)	195(25.8)	225
TB type							
PTB	33(4.4)	69(9.1)	17(2.2)	4(0.6)	9(1.2)	199(26.3)	331
EPTB	*	91(12.0)	27(3.8)	*	10(1.3)	297(39.3)	425

Rx: Treatment, PTB: pulmonary tuberculosis, EPTB: extrapulmonary tuberculosis, *: not applicable.

Table 2. Treatment outcome of seropositive tuberculosis patients by sex, age group, residence, and tuberculosis type (n = 191), Northwest Ethiopia, 2010 to 2012.

Characteristics	Treatment outcome						Total
	Cured N (%)	Rx completed N (%)	Died N (%)	Failure N (%)	Defaulted N (%)	Transferred out N (%)	
Sex							
Male	4(2.1)	17(8.9)	12(6.3)	*	*	61(31.9)	94
Female	3(1.6)	19(9.9)	17(8.9)	2(1.0)	2(1.0)	54(29.3)	97
Age in years							
0-5	*	*	*	1(0.5)	*	4(2.1)	5
6-11	*	1(0.5)	3(1.6)	1(0.5)	*	5(2.6)	10
12-17	1(0.5)	3(1.6)	1(0.5)	*	*	4(2.1)	9
18-23	1(0.5)	6(3.1)	1(0.5)	*	*	12(6.3)	20
24-29	2(1.0)	11(5.8)	4(2.1)	*	*	27(14.2)	44
30-35	2(1.0)	10(5.2)	10(5.2)	*	2(1.0)	28(14.7)	52
36-41	1(0.5)	2(1.0)	5(2.6)	*	*	11(5.8)	19
≥42	*	3(1.6)	5(2.6)	*	*	24(15.6)	32
Residence							
Urban	7(3.7)	33(17.2)	27(14.2)	2(1.0)	*	86(45.0)	155
Rural	*	3(1.6)	2(1.0)	*	2(1.0)	29(15.2)	36
TB type							
PTB	7(3.7)	19(9.9)	14(9.3)	2(1.0)	*	49(25.7)	91
EPTB	*	17(8.9)	15(7.9)	*	2(1.0)	66(34.5)	100

Rx: Treatment, PTB: pulmonary tuberculosis, EPTB: extrapulmonary tuberculosis, *: not applicable.

Table 3. Association between different factors, which may affect treatment outcome among tuberculosis patients (n = 756), Northwest Ethiopia, 2010 to 2012.

Characteristics	Successful treatment = 193 N (%)	Unsuccessful treatment = 563 N (%)	Total (N = 756)	RR (Risk ratio 95% CI)	P-value
Sex					
Male	119(26.9)	323(73.1)	442(58.5)	1.00	
Female	74(23.6)	240(76.4)	314(41.5)	1.1 (0.88-1.47)	0.311
Age (Years)					
≤29	138(29.5)	329(70.5)	467(61.8)	1.00	
>29	55(19)	234(81)	289(38.2)	1.6 (1.18-2.05)	0.004
Residence					
Urban	182(34.3)	349(65.7)	531(70.2)	1.00	
Rural	11(4.9)	214(95.1)	225(29.8)	7.0(3.89-12.62)	0.000
TB type					
PTB	102(30.8)	229(59.2)	331(43.8)	1.00	
EPTB	91(21.4)	334(78.6)	425(56.2)	1.4(1.13-1.84)	0.004
HIVserostatus					
Positive	43(22.5)	148(77.5)	191(25.3)	1.00	
Negative	139(24.6)	426(75.4)	565(74.7)	0.9(0.68-1.23)	0.625

DISCUSSION

The present study found that the successful treatment rate of all tuberculosis cases 193 (26%) treated at the DOTS clinic in Felege Hiwot Referral Hospital was not satisfactory. This finding can be contrasted to rates from the 2005 WHO report on global tuberculosis control, the treatment success rate among 22-high burden countries varied from 60% in Uganda to 93% in China, with an average of 83% (WHO, 2005). Likewise, in 2011, the study conducted by Chennaveerappa et al. (2011) in India has reported a treatment success rate at 83%. Furthermore, a study conducted in the southern part of Ethiopia showed that the treatment success rate of all tuberculosis cases was 49% (Shargie and Lindtjörn, 2005).

Ramose et al. (2008) and the NTLCP reported 70 and 78% treatment success rates, respectively (MOH, 2008). The low treatment success rate observed in the present study might be due to the high transferred-out rate (65.6%); it is impossible to know the treatment outcome for patients who were transferred out. Concurrent with other studies conducted in India (Chennaveerappa et al., 2011; Faustini et al., 2005), this study also found a death rate of 5.8%. Moreover, the death rate of patients steadily increased in older age groups. Similar findings were reported from the studies conducted in Gondar University Hospital, northwest Ethiopia (Tessema et al., 2009), southeast Ethiopia (Ramose et al., 2008), and Eastern Taiwan (Jyh Lee et al., 2007). Older age has been reported to be a risk factor for death due to lowered immunity and co-morbidities (Cayla et al., 2004). The defaulter rate in this study (2.5%) was lower than in other studies conducted elsewhere in the country 11.3, 36.4% and 6% (Ramose et al., 2008; Tessema et al., 2009; Yassin et al., 2003), respectively. Ditah et al. (2008) reported 20% defaulter rate. This lower defaulter rate in this study might be due to proper supervision and health education in the study area.

In this study, the high death rate (3.3%) and treatment default rate (1.5%) that were recorded for female patients deserves special attention. Strengthening monitoring, supervision, and health education to reduce deaths and treatment interruption in females should be among the top priorities in the study region.

Ditah et al. (2008) reported that the treatment failure rate in Zimbabwe and in other high TB burden countries was 0.1 and 1.5%, respectively. Tessema et al. (2009) also reported only a 0.2% treatment failure rate, while there were 0.5% treatment failures in the patients of our study group. In this study, the patients from rural areas had a significantly lower treatment success rate compared to patients from urban areas (RR = 7.0, 95%CI = 3.89 to 12.62, $p = 0.000$); the lower treatment success rate in rural patients is probably due to lower awareness of TB treatment and the long distance between their homes and the treatment center (Ramose et al., 2008).

Close monitoring and health education for rural patients is of great importance. The patients in the mean age groups greater than 29 had a significantly lower treatment success rate compared to other age groups (RR = 1.6, 95%CI = 1.18 to 2.05, $p = 0.004$); older age has been reported to be a risk factor for death, partly due to co-infection and general physiological deterioration with age, and thus it is crucial to exercise close monitoring of TB treatment also in older patients (Tessema et al., 2009). Patients with PTB had a significantly higher treatment success rate compared to patients with EPTB (RR = 1.4, 95% CI = 1.13 to 1.84, $p = 0.004$). This might be due to delayed diagnosis of EPTB patients, which we suspect increases tuberculosis mortality.

HIV infection increases the chance of tuberculosis reactivation and infection (Ramose et al., 2008). In this study, the HIV prevalence rate of 25% recorded among TB patients is much lower than in the previous reports from Gondar of 52.1% (Kassu et al., 2007), and higher than in reports by Ramos et al. (2008) (1.7%). The present study found that the treatment success rate of all TB-HIV co-infection cases treated under the DOTS program at Felege Hiwot Referral Hospital was 23% ($n = 191$). The death rate among TB-HIV co-infection was 15.2%, the failure rate was 1%, and defaulted rate was 1.0%, indicating that special attention to HIV-positive TB cases is required in the study region. The present study demonstrated that patients with PTB-HIV co-infection were more likely to have favorable treatment outcome (13.6%) than EPTB-HIV co-infection cases (8.9%), possibly because their illness is more severe and symptomatic (Tekle et al., 2002). Though not statistically significant, this study showed that the treatment success rate for HIV negative tuberculosis patients 24.6% ($n = 139$) was higher than for HIV positive patients 22.5% ($n = 43$), indicating that HIV testing before treatment is crucial.

These findings are subject to at least three limitations. First, selection bias, second, the hospital is a referral hospital and patients came from other health facilities to be diagnosed. Third, the patients were then admitted to the hospital and after finishing the intensive phase, transferred out to their nearby health facilities. Thus cured, failure, default and death were not detected. Nevertheless, our study tried to provide base line information about treatment outcome of TB patients. The results of this study also indicate that TB is still a major public health problem in Felege Hiwot Referral Hospital.

Conclusion

The treatment success rate of tuberculosis patients treated at the Felege Hiwot Referral Hospital DOTS clinic in northwest Ethiopia was not satisfactory (26%). A high proportion of patients were transferred out (65.6%), (5.8%) died, (0.5%) failed, and (2.5%) defaulted. The percentage of deaths and defaulters was higher in females

than in males, and patients from rural areas had a significantly lower treatment success rate compared to cases from urban areas, which are serious public health concerns that need to be addressed urgently. Also, we were able to demonstrate from our data that HIV negative patients being treated for TB were associated with better treatment outcome. We conclude that treatment plans that emphasize DOTS for at-risk patients have the greatest success in improving tuberculosis treatment outcome in the region. Urgent need for strengthening a coordinated tuberculosis control program and treatment outcome monitoring is strongly recommended. Future research should be done to identify causes of a common reason for unsuccessful treatment outcome in TB patients.

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