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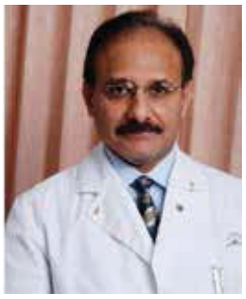

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Editorial

Cough, Cough, Cough: Should I Prescribe a Cough Medicine?

I am sure to the older generation this question is a no brainer but to the younger doctors who were born after the era of evidence or should I say 'error' of evidence then a real quagmire exists. They were born in a world full of cough mixtures and probably have been forced to swallow one when they were young, so they have a practical experience of these medicines. I have always wondered, of what use is the data / experiences we have before they become scientifically proven evidence? That guts feeling, the sixth sense, the *de javu* etc that has been part of you for years! Do you just let it go because evidence does not recognize it?

Cough is serious business, if you do not believe me ask otolaryngologists and pulmonologists. I even dare say that it is more common than pain in most general practice offices. Even the world largest economies the USA, billions of dollars are spent every year on over-the-counter cough medicine(1).

Interestingly, I do not remember being taught a topic on cough syrups in medical school. Is it just me with my truant behavior that missed this class? How could my teachers fail me this badly? My assertion still remains that most doctors learnt about cough syrups from their mothers in child hood and medical representatives upon graduating.

Ever wondered what were the origins of the cough syrups? The cough medicine is actually a home remedy developed in the medieval times to sooth the throat in coughing patients. In other words cough syrups are an advance version of the famous mummy's concoction of hot water, lemon, honey and ginger spike with a tinge of whiskey for the over 18 years of age now put in a beautiful bottle! Seriously some still contain some alcohol, while others have added additive drugs with fancy names like cough suppressants and expectorants. These home remedies backed by aggressive pharmaceutical marketing have ensured that all patients demand for them or buy them off the counter.

Does the world need cough syrups?

The fact is that coughs cause a lot of misery, sends more than 30 million people to the doctor every year. Most of us have experienced this, the bad cough that gives you lots of chest pain, leads to vomiting, bouts leading to breathlessness etc and all you want is for it to stop despite the underlying cause! Interesting last week I attended a lady who had coughed badly during the senior management meeting that she was immediately sent of sick leave. Guy's social stigma is real, the society equates a coughing to dangerous/contagious diseases including tuberculosis and even corona virus 2019(2)!

Cough is usually a protective reflex that is meant to throw out offending intruders out of the lungs. At times cough may result from a reduced oxygen/ air reaching the blood and the brain falsely interprets this as an airway blockage needing clearance. Worse is when there growths in the airway lead to a continuous irritation leading to prolonged exhaustive cough without much benefit. This is the theoretical reason of wanting to suppress the cough. Even musicians have not been left behind and have composed a song on this bad cough; see lyrics at: *https://www.metrolyrics.com/cough-syrup-lyrics-young-the-giant.html.* The world badly needs an effective cough treatment, but there is no rigorous research in new effective cough drugs and all we are left with are the vintage improvements of the home remedies(2).

Is there any scientific evidence that cough syrups work?

Pharmaceutical companies have lead us to believe that cough syrups reduce the intensity and length of cough and consequently coined the name anti-tussives commonly known as cough sedative/ suppressants such as codeine and pholcodeine all being central acting opoid derivatives and as such come with the attendant side effects and risk for abuse and dextromethorphanan non opoid analogue with less potential for addiction and abuse. They have also created a group called expectorants that supposedly hasten removal of the murky sputum from your lungs including guafenesin, bromohexine etc, but do they work when used correctly(3)?

Smith *et al* (1) in a Cochrane review of over the counter medications for acute cough in children and adults in ambulatory settings published in the Cochrane Database Systemic Reviews 2008 January 23rd included twenty five trials (17 adults, 8 children) involving 3492 people (2876 adults and 616 children)(4). Studies in adults; Six trials compared antitussives with placebo and had variable results. Two trials compared the expectorant, guaifenesin with placebo, one indicated significant benefit whereas the other did not. One trial found that a mucolytic reduced cough frequency and symptom scores. Two studies examined antihistamine-decongestant combinations and found conflicting results. Three studies compared other combinations of drugs with placebo and indicated some benefit in reducing cough symptoms. Three trials found antihistamines were no more effective than placebo in relieving cough symptoms. Studies in children; Antitussives (two studies), antihistamines (two studies), antihistamine decongestants (two

studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. No studies using expectorants met our inclusion criteria. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group. This lead the author to conclude that "There is no good evidence for or against the effectiveness of OTC medicines in acute cough. The results of this review have to be interpreted with caution due differences in study characteristics and quality. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self-care treatments for acute cough (4)". The summary of the studies is in Tables 1-3.

Table 1: Studies with codeine

Study	Sample size	Design	Disease	Results
Eccles R, *et al*. Lack of effect of codeine in the treatment of cough ssociated with acute upper respiratory tract infection. *Journal of Clinical Pharmacy and Therapeutics* 1992; 17(3): 175-80.	81 adults	Not reported	URTI's	Codeine was no more effective than placebo either as a single dose or in a total daily dose of 120 mg, reported on a five-point cough severity score (P > 0.2)
Freestone C *et al.* Assessment of the antitussive efficacy of codeine in cough associated with common cold. *Journal of Pharmacy and Pharmacology* 1997; 49:1045-9.	82 adults	A double blind, stratified, placebo-controlled, parelleled-group.	URTI's	The results demonstrate that codeine is no more effective than placebo in reducing cough associated with acute URTI, as measured by CSPLs, cough frequency of subjective symptom scores

Source: De Blasio F, Virchow JC, Polverino M, Zanasi A, Behrakis PK, Kilinç G, Balsamo R, De Danieli G, Lanata L. Cough management: a practical approach. *Cough*. 2011 Oct **10**;7(1):7. doi: 10.1186/1745-9974-7-7. PMID: 21985340; PMCID: PMC3205006 (5).

Table 2: Clinical studies with dextromethorphan

Study	Sample Size	Design	Disease	Results
Lee PCL *et al*. Antitussive efficacy dextromethorphan in cough associated with acute upper respiratory infection. *Journal and Pharmacology* 2000; **52**: 1137-42.	44 adults	A double-blind, stratified, randomized and parallel group design	URTI's	This study provides very little if any support for clinically significant antitussive activity of a single 30 mg dose of dextromethorphan in patients with URTI's
Parvez L, *et al*. Evaluation of antitussive agents in man. *Pulmonary Pharmacolog* 1996; **9**(5-6)299-308.	451 adults	Review of three different studies randomized, double blind, placebo controlled	URTI's	The results establish the sensitivity and robustness of the cough quantization methodology in the objective evaluation of cough tratments
Parvez L, *et al*. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analsis. *Chest* 001;120:1121-8.	710 adults	Six studies used for the meta-analysis were randomized, double-blind, parallel-group, single-dose, placebo-controlled studies with 3-h postdose cough evaluation period	URTI's	The results of a meta-analysis show that the antitussive effect of a single dose of dextromethorphan hydrobromide, 30 mg, has been established

Source: De Blasio F, Virchow JC, Polverino M, Zanasi A, Behrakis PK, Kilinç G, Balsamo R, De Danieli G, Lanata L. Cough management: a practical approach. *Cough*. 2011 Oct **10**;7(1):7. doi: 10.1186/1745-9974-7-7. PMID: 21985340; PMCID: PMC3205006 (5).

How about peripheral acting antitussives such as levodropropizine?

Table 3: Clinical studies with levodropropizine vs central antihissives in children

Study	Sample Size	Design	Disease	Results
Banderai! *et. al J Ini Med Res* 1995 May-jun; 23(3): 175-83	254 children aged between land 14yrs	Double blind randomized Dropropizine vs Levodropropizin	Non-Productive Cough	There were statistically significant decreases in the frequency of coughing spells and nocturnal awakenings after both LDP and dropropizine treatments with no statistical difference between both group. Somnolence was twice as frequent in the dropropizine group (10.3% vs 5.3%) and the difference is clinically relevant though not statistically significant
Dong Soo Kim *et al.* Diagnosi*, and Treatment Voi 22. Num 9. 2002	77 children aged 2 and 3 years	Double blind randomized LDP vs Dextromethorphan	Bronchitis	The results show the antitussive effectiveness of LDP and point out a more favourable benefit risk profile when compared with dextromethorphan.
Flocchi *et al*. *Ped Med Chir* 1989	70 children, age ranged between 2 months and 14 years	Open Label	Respiratory tract disease	- The treatment was effective on 69.70 children. No child showed a worsening in the cough after 24 hours treatment.
Tamburrano *et al*. *Terapie ssenziali in clinica* 1989; 3-7	180 children aged between 5 months and 12	Open Label	Respiratory tract disease	- The results of the present study prove that the treatment with LDP in children is excellently tolerated and clinically active
Banderai *et al* Study LPD 0191. Data on file Unplublished	325 children aged between 2 and 14 years	Open label	Non-productive	- This study proved the a favourable therapeutic results with limited risk of inefficacy, with the subsequent improvement in the patient's and parents' quality' of life, and with remarkably limited risk of intolerance, especially in terms of daytime somnolence.

These seem to show more promise that the central acting drugs with better cough reduction scores and the much needed peace and quiet to the parents (6).

Always remember when it comes to cough syrups science is playing catch up. These were drugs meant to offer relief or rather sooth the throat, so how do we evaluate such drugs? Most scientists believe an end point like cough intensity and length are erroneous because they were not the initial aims for such drugs. They were not expected to shorten the length of cough but to reduce the pain and discomfort related to cough. Please note this was not the original target of the home remedies as the pharmaceutical industry has made us think.

Also note that these studies don't say cough medicines don't work but that they found no proof that they work in URTis. It's always possible that further studies could show their benefit and they may be useful in other conditions other than URTIs. Newer cough targets such as TRP receptor blockers are under research and just be our magic bullet in cough (3).

So was it an overreaction fuelled by a lack of good evidence that cold and cough medicines help despite a very small risk of serious side effects that the FDA in 2008 advised against the use of these medicine in toddlers and babies below 4 years? And the American Academy of Pediatrics pushed it even further to children under 6 years of age? The odds of serious side effects in older children and adults is very small, with an exception of those with a medical condition such us hypertension or heart disease that need a doctors clearance (8-12).

Diseases such as bronchiectasis, ciliary dykinesia, chronic bronchitis etc patients cough and expectorate viscid mucous, would cough mixtures be useful? Weupe *et al* (12) in their concept paper 'Moving mucus matters for lung health", states that mucus build up in the lungs provides a good environment for bacteria, fungi and viruses to thrive with deletious effects. Theoretically any medicine that will limit mucus buid up would be beneficial (13).

Olivieri *et al* (13) in their study (n=88) reviewed the addition of bromhexine hydrochloride to an antibiotic during an acute infective exacerbation compared with a placebo. It is thought this medication may influence sputum clearance by increasing the production of serous mucus thereby making the sputum thinner and less viscous. Results suggest that this medication was effective, as the percentage change in sputum production was greater in the bromhexine group at 7, 10 and 16 days (mean difference (MD) −21.5 mL, 95% CI −38.9 to −4.1 at day 16). Moreover the difficulty in expectoration was also improved in the bromhexine group at day 10 (MD −0.53, 95% CI −0.81 to −0.25) however it had no impact on FEV1 (14). Bromhexine hydrochloride is not widely available in the UK and is not listed in the BNF.

Erdosteine is another mucolytic which is thought to modulate mucus production through the scavenging activity of free radicals. Crisafulli *et al* (14) in a study in 2007 compared the use of erdosteine and respiratory physiotherapy to respiratory physiotherapy alone over a 15 day period in a bronchiectasis population (n=30). This study was small and of poor methodological

quality due to limited control of bias. Small changes were seen in some subjective sputum characteristics and FEV1 in the erdosteine group (6).

Obliviously overuse of cough syrups is not warranted and mixing various cough mixtures is not a wise thing to do. Opoid additives lead to addiction and should be discouraged and prolonged use of such medicines is not beneficial. Lastly, before prescribing a cough syrup remember, coughing may be good for your patient, helping the lungs remove out excess mucus and other irritants in a natural way.

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Original paper

Factors that Influence Pneumococcal Vaccine Uptake among Children Aged 14-52 weeks in Uasin Gishu County, Kenya

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Abstract

Background: The Pneumococcal Vaccine Serotype 10 (PCV10) was launched on the 14th of February 2011 in Kenya under the Division for Vaccination and Immunization (DVI) program at the Ministry of Health (MoH). PCV10 is a part of the immunization schedule for under-fives and is offered in three doses alongside the pentavalent vaccine. Upon its launch, the PCV10 was expected to lower mortality and morbidity due to streptococcal infections in under-fives. However, to date, its uptake and factors that influence its uptake have not been studied sufficiently in rural areas.
Objectives: To evaluate the factors influencing the uptake of the pneumococcal PCV10 vaccine among children aged 14-52 weeks in Uasin Gishu, Kenya.
Design: This was a descriptive cross-sectional study.
Methodology: The study was done in Huruma Estate in Uasin Gishu County, Kenya. Cluster sampling was used to recruit 185 children aged 14-52 weeks and a structured questionnaire used to interview caregivers on the immunization history of children. The socio-demographic data of children and caregivers and the knowledge and attitudes of caregivers on the PCV10 vaccine evaluated. Data analysis was done using version 21 of the Statistical Package for Social Scientists (SPSS). Questionnaires were screened for inconsistencies and data extracted and coded in SPSS. Socio-demographic data were explored, PCV10 uptake computed, and the chi-square test and logistic regression used to determine factors that influence the uptake of the PCV10.
Results: The uptake of the PCV10 vaccine was 96.8%. The awareness of the PCV10 among caregivers was 68.7%, a majority of whom (68%) gained knowledge from health facilities. Awareness was higher among caregivers with a primary education (OR (CI) = 2.6 (1.26 - 5.3), $p<0.05$) and youths (OR (CI) = 2.39 (1.3 - 4.6), $p<0.05$). However, the age, marital status, and the education level of caregivers and social factors such as the distance to the immunization site and behavior of facility staff did not statistically influence uptake significantly ($p>0.05$).
Conclusion: The uptake of the PCV10 in Huruma was 96.8%, which was higher than the national rate of 86%. Knowledge of PCV10 and attitudes towards immunization were good. However, knowledge, attitudes, socio-demographic characteristics of caregivers and children, or the social factors studied were not associated with the uptake of the PCV10 vaccine.

Key words: PCV10, Pneumococcal vaccine, Pneumonia, Knowledge

Introduction

Pneumonia is a common infectious disease of children, whose commonest causative agent is *Streptococcus pneumonia* (1). According to the World Health Organization (WHO), it is the leading cause of death worldwide for under-fives with about one million deaths reported every year (2). In East Asia and the Pacific, pneumonia accounted for 16% of deaths of children under five in 2008. In the same year, 14% of deaths of under-fives in sub-Saharan Africa (SSA) and 16% of neonatal deaths in Kenya were due to pneumonia despite it being a preventable disease (3). At the Eldoret District Hospital, the morbidity and mortality rates of under-fives with pneumonia were 26.8% and 20.4% respectively in 2018 (4).

In 2000, the Pneumococcal Conjugate Vaccine serotype seven (PCV7) was launched in the United States of America (USA). This resulted in the reduction of pneumonia-induced morbidity in under-fives and under-twos by 77% and 39% (5). By 2003, uptake of the PCV7 was 69%, with its availability cited as the main predictor for its utilization (7). By August 2008, 26 countries had integrated the PCV7 in immunization schedules, with its uptake estimated to 50% (5,6). However, since the PCV7 was ineffective against some serotypes of *Streptococcus pneumoniae*, it was replaced by a decavalent vaccine in 2012, PCV10, which was effective against ten serotypes of the pneumococcus namely 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F (7).

In 2007, the first formal meeting on the WHO and UNICEF yielded the Global Action Plan for Prevention of Pneumonia (GAPP), with pneumococcal vaccination as its cornerstone. GAPP proposed that countries should achieve 90% uptake of the pneumococcal

vaccine by 2015 to attain the Millennium Development Goal (MDG) number four of 2000 – reducing child mortality in United Nations (UN) countries by 75%. In 2001, uptake of the pentavalent vaccine in Mathare, Kenya was 62.2%, with poor knowledge, negligence, and the costs associated with access to the PCV7 increasing non-compliance (8). However, since the adoption of the PCV10 on 14th February 2011, its uptake in a rural setting such as Huruma has not been explored sufficiently, although it is part of the DVI with the pentavalent vaccine.

Materials and methods

This was a descriptive cross-sectional study in Huruma Estate – a peri-urban settlement in Uasin Gishu County, located 7 km from Eldoret town. Children aged 14-52 weeks were targeted. According to the Ministry of Health (MoH), the administration of the final dose of the pneumococcal vaccine should be at 14 weeks. However, by the time we were doing the study, children who had received the pneumococcal vaccine in 2011 had attained the age of two years, hence the upper limit of 52 weeks. Consent was sought from a parent or a caregiver for a child to qualify for the study.

Cluster sampling was used to recruit 185 children. The study site was divided into five clusters and two clusters were chosen randomly. Households with children aged 14-52 weeks were identified, consent administered, and participants recruited until the sample size was attained. An interviewer-administered questionnaire was used to collect data. The socio-demographics of caregivers and immunization history of children were captured. The knowledge and attitudes of caregivers on PCV10. To compute attitude scores, six questions evaluating the perceptions of caregivers on the PCV10 were administered and scored as 1 for a good perception and 0 for bad. Then, an overall attitude score was generated, a cumulative attitude score (%) calculated for participants, and scores interpreted as described by Rubaish (9). At 60% cut-off, participants with a cumulative score of <60% were deemed to have a bad attitude while those with a cumulative score ≥60% a good attitude towards the PCV10. Social factors that influenced access to the PCV10 vaccine were also captured on the questionnaire.

Data analysis was done using version 21 of the Statistical Package for Social Scientists (SPSS) software. Questionnaires were scrutinized for inconsistencies such as missing data, errors, and omissions and participants with >20% missing data eliminated. Then, data were coded in an SPSS worksheet, and frequency distributions explored. The uptake of the PCV10 vaccine was evaluated and computed following the guidelines of the Centers for Disease Control (CDC). To test attitudes on PCV10, six questions were scored as 0 for negative responses and 1 for positive responses. The scores were summed into an attitude score and scores interpreted as 0–3 for negative attitude and 4-6 positive attitudes. Correlation analyses were done to identify the factors that influence the uptake of the PVC10.

Results

Demographic characteristics

a) *Caregivers:* One hundred and eight-five participants comprising mothers, fathers, and providers of care were recruited and interviewed. Mothers (n=179) constituted 76% of our respondents. Most caregivers were aged between 20 and 34 years 90 (48.6%), married 168 (90.8%), and had a primary level of education 91(49.2%) (Table 1).

Table 1: Socio-demographic characteristics of caregivers (N=185)

Age (year)	Frequency	(%)
18-24	87	47.0
25-34	90	48.6
35-44	7	3.8
45+	1	0.5
Sex		
Male	4	2.2
Female	181	97.8
Marital status		
Single	14	7.6
Married	168	90.8
Separated	1	0.5
Widowed	2	1.1
Occupation		
Self-employed	58	31.4
Unemployed	106	57.3
Employed	21	11.4
Education		
Primary	91	49.2
Secondary	73	39.5
Tertiary	19	10.3
None	2	1.1

b) *Children:* One hundred and eight-five children were recruited. Most were aged 12-52 weeks 85 (45.9%), male 99 (53.5%), and had siblings 116 (62.7%) – mostly one 68 (36.8%) (Table 2).

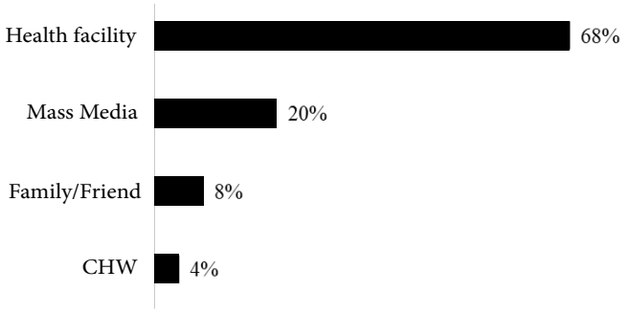
Table 2: Socio-demographic characteristics of children (N=185)

	Frequency	(%)
Age (weeks)		
<24	33	17.84
24-48	67	36.22
49-96	85	45.95
Sex		
Male	99	53.51
Female	86	46.49
Presence of siblings		
Yes	116	62.70
No	69	37.30
No. of siblings		
0	67	36.22
1	68	36.76
2	30	16.22
3	12	6.49
4	5	2.70
5	3	1.62

Immunization

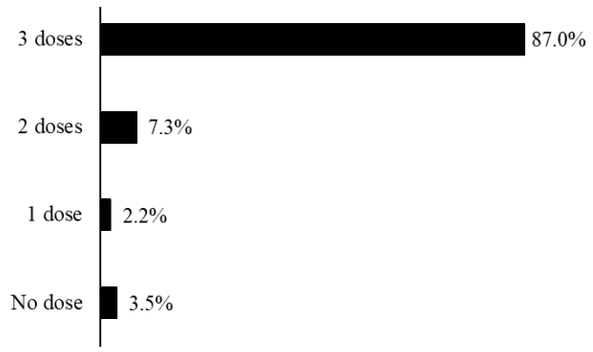
a) *PCV10 awareness:* Approximately 127 (68.7%) of respondents were aware of the PCV10 pneumococcal vaccine. Of those who were aware, 95 (74.8%) were knowledgeable on the mode of administration of the PCV10, while 93 (73.2%) knew the correct number of doses that should be administered to children. A majority of respondents 86 (72%) gained information about the vaccine from health facilities, while 26 (20.5%) were informed by mass media such as the radio and television. Community Health Workers (CHWs) informed only 4% of subjects (Figure 1).

Figure 1: Source of information on PCV10 pneumococcal vaccine



b) *PCV10 uptake:* At least 179 (96.8%) of children received at least one dose of the PCV10 pneumococcal vaccine. However, only 124 (67.0%) of cases were confirmed from the MoH immunization card. About 161 (87.0%), 14 (7.6%), and 4 (2.2%) received three, two, and one dose (Figure 2). Lack of knowledge 3 (12.5%), delay in immunization 6 (25.0%), and lack of vaccines 6 (16.7%) were the most typical reasons for non-compliance to the immunization schedule.

Figure 2: Dosage for the PCV10 vaccine



c) *Attitudes towards immunization:* Most respondents, 184 (99.5%) had a positive attitude towards pneumococcal immunizations. Even though caregivers with a negative attitude were more likely to skip vaccinations (r=-0.013), attitude did not influence the uptake of the PCV10 vaccine significantly (p=0.855).

Factors that influence PCV10 uptake

Socio-demographic characteristics of caregivers were not associated with non-compliance with immunization. The age (p=0.861), marital status (p=0.611), occupation (p=0.800), and educational level (p=0.087), did not influence uptake of PCV10 significantly. The attributes of children and social factors analyzed were not associated with PCV10 uptake, (Table 2).

Table 2: Link between caregiver and children attributes and social factors on PCV10 uptake

	Uptake of PCV10	
	r	P-value
Caregiver's attributes		
Age	0.013	0.861
Marital Status	0.038	0.611
Occupation	0.019	0.800
Education level	-0.126	0.087
Children's attributes		
Age	0.108	0.144
Presence of siblings	0.048	0.516
No. of siblings	0.010	0.893
Social factors		
Distance to immunization site	0.062	0.402
Behavior of facility staff	0.060	0.416
Unavailability of vaccine	0.105	0.154

Discussion

The uptake of PCV10 in Huruma Estate in Uasin Gishu County was 96.8%, which was 10.8% higher than uptake of the pentavalent vaccine nationally (86.0%) (10). This was in contrast to the findings of Kamau *et al*. (8) in 2001 in which uptake of the pentavalent vaccine in Mathare Valley, Nairobi was 62.2%. The high uptake of the PCV10 might be because the PCV10 was administered with a pentavalent vaccine during postnatal clinics and thus had an already-established immunization schedule. In most cases, health care workers administered PCV10 alongside a pentavalent whether they were knowledgeable about it or not. Moreover, 68% of caregivers were knowledgeable on PCV10, 99.5% of whom had a positive attitude, and were knowledgeable of the immunization schedule, which improves acceptance of new aspects of healthcare (11,12). Parents with a positive attitude towards immunization and have access to health care have also been reported to consider vaccination as a requirement for all children and are willing to return later for vaccinations during vaccine stock-outs. Because health facilities were the primary source of education for caregivers, there is a need to beef up health education in national and county hospitals to boost the awareness of PCV10 further.

In a study by Danis *et al.* (13) maternal age and the education level of caregivers had an inverse relation to the uptake of the PCV10. Also, Kamau *et al*. (8) reported that children born to married women were more likely to complete immunization schedules as required. However, we found different results. Demographic characteristics of caregivers such as age, marital status, and education level did not influence the uptake of the PCV10 statistically. Moreover, demographic characteristics of children and social factors such as the distance to immunization site, the behavior of staff, and the availability of vaccines did not influence the uptake of the PCV10 vaccine statistically. However, because the sample size was small, we could have underestimated the relationship between demographic and social factors studied and uptake of PCV10 in Huruma in Uasin Gishu County in Kenya. Follow-up studies with a larger sample size are required to corroborate our findings or show statistical differences.

Conclusion

Uptake of the pneumococcal vaccine, PCV10, is almost universal (96.8%) in Huruma Estate of Uasin Gishu County, Kenya and slightly higher than the national uptake of the pentavalent vaccine (86%). Awareness of the PCV10 was high, with a majority of caregivers having a positive attitude on immunization. The socio-demographic characteristics of caregivers and children and social factors of the study area did not influence the uptake of PCV10 vaccine.

Conflict of interest

The authors have declared no conflict of interest

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Original paper

Prevalence and Correlates of Depression among HIV Infected Patients on Highly Active Antiretroviral Therapy in a Kenyan Referral Hospital

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Abstract

Background: Human Immunodeficiency Virus (HIV) infected patients are 2-3 times more likely to suffer from depressive disorders compared to non-infected individuals. Furthermore, depressive disorders are associated with lower adherence, poorer clinical outcomes and increased risk of HIV transmission behavior. However, screening for depressive disorders is not routinely done in most HIV management centres in the public sectors of resource-constrained countries. As such, research into the extent to which depressive disorders and the associated clinical determinants required to be undertaken.

Objective: To determine the prevalence and risk factors for depression among HIV infected patients on highly active antiretroviral therapy at the Kenyatta National Hospital.

Methods: This was a cross sectional study among 345 HIV positive patients on Highly Active Antiretroviral Therapy (HAART) at the HIV comprehensive care centre between July 2015 and August 2015. Baseline participants' socio-demographics were obtained through interviewer administered questionnaires while the clinical data was abstracted from patient records using a predesigned data collection tool. The 9 item Patient Health Questionnaire (PHQ-9) was used to assess the level of depression. Descriptive and inferential data analysis was done using R® statistical software.

Results: The mean age of the study population was 42.0 (±.9.5) years, with a female: male ratio of 1.4:1. Prevalence of depression disorders was at 20.6%, constituting minimal symptoms (17.7%), mild depression (2.0%), moderate depression (0.6%), and severe depression (0.3%). More females (63%; n=45) than males suffered from depression, though this was not statistically significant (p=0.354). Prolonged use of antiretroviral therapy was protective against depression (aOR = 0.85, 95% CI [0.73, 0.98], p=0.005) whereas being co-morbid with hypertension increased the risk (aOR = 5.20, 95% CI [1.52, 32.68], p=0.027).

Conclusion: A fifth of patients on HAART suffer from depressive disorders, which are compounded by comorbidities such as hypertension. Clinicians should be encouraged to routinely screen for depression among HIV infected patients particularly in the early phases of treatment. Extensive studies are required to correlate ARV regimens, serum antiretroviral drug concentrations and adverse drug reactions with mental illness among HIV infected patients.

Key words- Depression, HIV infected, HAART, PHQ-9

Introduction

HAART has enabled HIV positive patients on treatment to continue living longer (1,2) and the focus is gradually shifting towards detection and optimal management of non communicable co-morbid conditions such as depression. Interestingly, mental illness among HIV positive patients is now an emerging concern in sub Saharan Africa. Furthermore, depression is the most common psychiatric illness encountered, with a two to three-fold higher prevalence among people living with HIV compared to HIV negative controls (3,4).

Possible neurobiological explanations for the higher risk of depressive illness among HIV positive patients include persistent neuroinflammation, presence of toxic viral proteins within the Central Nervous System (CNS), cytokine-induced basal ganglia dysfunction, as well as enhanced degradation of tryptophan, leading to reduced serotonergic transmission within the brain (5-7). Psychosocial factors, such as stigmatization and living with the constant fear of premature death are also integral components which have been proposed to precipitate mental illness among HIV infected individuals (8).

The consequences of untreated depression among HIV positive patients are deleterious. Apart from reduced productivity, social isolation and impaired quality of life, depression has been associated with reduced ART adherence (9,10), increased suicidal ideation (11), body weight reduction , slower CD4 cell restitution, faster progression to full blown AIDS, and higher overall mortality (12,13).

Symptoms of depression can occur during any stage of HIV (14), pointing towards a need for constant screening of infected individuals. Importantly, early diagnosis and treatment of depressive illnesses among HIV positive patients has been associated with improved ART adherence, increased psychosocial function, and improved overall quality of life(15). Worryingly, prevalence rates of depressive illnesses of upto 65% among HIV positive patients have been reported in Cameroon, with depressive illnesses found to be associated with concomitant alcohol abuse and severe immunosuppression (16).

The present study aimed at determining the prevalence of depressive disorders and the associated risk factors among HIV infected participants on HAART in a leading Kenyan teaching and referral hospital.

Materials and methods

Study design: This was a cross sectional survey among HIV 1 positive patients on follow up at the Kenyatta National Hospital Comprehensive Care Clinic (KNH-CCC). KNH is the largest teaching and referral hospital in East and Central Africa, and runs a daily comprehensive care clinic catering for low and middle income earners drawn from Nairobi county and its environs.

Study population: Patients with documented HIV 1 positive infection on antiretroviral therapy, who were 18 years or older, and who signed informed written consent to participate were consecutively recruited into the study. Patients were excluded if they had head injury, CNS opportunistic infections, seizure disorders, history of other psychiatric illness such as schizophrenia and substance abuse. Patients with medical illnesses such as chronic renal failure, chronic liver disease, and malignancy which are likely to cause neurological sequelae were excluded.

Sample size: A target sample size of 329 was estimated using the Fisher *et al* formula with consideration of similar studies carried out elsewhere in Africa (17). An additional 5% was recruited in case of non-completeness of data.

Study procedures: Human Immunodeficiency Virus (HIV) positive patients on ART who met the inclusion criteria were consecutively recruited into the study after giving informed written consent. Research staff administered standardized case report forms and reviewed patients' files to collect data on demographics and clinical history. Self-administration of the Patient Health Questionnaire-9 (PHQ-9) was done after acquisition of participants' socio-demographic and clinical details.

The PHQ-9 is a questionnaire used in screening for depressive illness, and consists of 9 questions, each with a score of between 0 and 3 points. Domains scored include loss of interest/pleasure in doing things, feelings of hopelessness, asthenia, changes in appetite, feeling bad about oneself, problems with concentration, slowed movements, and suicidal ideation. Scores are given depending on how often one has perceived these feelings over the preceding two weeks, with a score of 0 if not at all, 1 if they occurred on several days, 2 if they occurred more than half the days, and 3 if they occurred nearly every day.

A total score of 1-4 was then graded as minimal depression, 5-9 as mild depression, 10-14 as moderate depression, 15-19 as moderately severe depression, and 20-27 as severe depression. The PHQ-9 has been validated as an instrument capable of screening for criteria-based diagnoses of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) depressive disorders (18), as well as measuring severity of depression (19). Using a cut-off score of ≥10, the PHQ-9 had a sensitivity of 88% and specificity of 88% for major depression (19). Further, it was found to be both valid and reliable as a depression screening tool among HIV positive patients in rural Western Kenya (20).

Ethical considerations: The study received ethical approval from the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (Reference KNH-ERC/1/136).

Data analysis: Data collected was entered into a database created using Epi Info (version 7, CDC, Atlanta, GA, USA). Statistical analysis was performed using R® (version 3.2.5) statistical software. Categorical variables were detailed in frequency tables while continuous measures were summarized using means and standard deviations or medians and ranges, as appropriate. After assessing for normality with Shapiro Wilk test, plotting histograms and QQ plots, t-test was used to determine the strength of associations in mean values for continuous variables and chi-square tests for binary variables.

To determine the covariates for prevalence of depression, logistic regression modelling was conducted using backward stepwise selection to identify parameters to fit in the final model. The threshold for statistical significance was set at $\alpha = 0.05$.

Results

Three hundred and forty five participants were recruited into the study, with a female : male ratio of 1.4:1 (Table 1). The mean duration on antiretroviral therapy was 5.6 years (SD ±3.4). The mean age of the study participants was 42 years (SD ±9.5) and the median CD4 count was 446cells/mm^3 (IQR 278-596). Viral load tests results were available for only 53 participants, majority (53%) of whom were virally suppressed. Hypertension was observed in 13% of the participants (Table 2).

Table 1: Baseline socio-demographic characteristics of participants

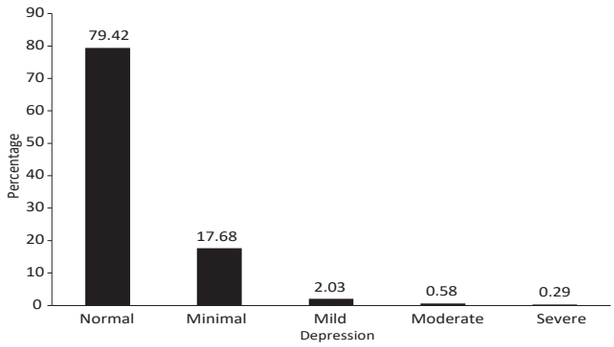
Characteristic	No.	(%)
Sex		
Male	143	41
Female	202	59
Marital status		
Single	79	23
Married	205	59
Separated	14	4
Divorced	9	2
Widowed	38	11
Occupation		
Unemployed	29	8
Self employed	193	56
Employed	120	35
Student	3	1
Smoking status		
Smoker	10	3
Non smoker	335	97
Consumes alcohol		
Yes	34	10
No	311	90

Table 2: Baseline clinical characteristics of the participants

Characteristic	No.	(%) or mean(SD)
Hypertensive		
Yes	45	13
No	300	87
Diabetic		
Yes	14	4
No	331	96
CD4 count		
<250	74	22
250-349	49	14
350-499	86	25
≥500	132	38
Missing	4	1
Viral load (n=53)		
Suppressed (<400 copies/ml)	28	53
Unsuppressed (≥400)	25	47
Mean months since CD4 was done	341	15 (13)
Mean years since last viral load	53	1.9 (1.3)
Mean years since HIV diagnosis	345	6.3 (3.7)
Mean years (SD) on ART	345	5.6 (3.4)

The prevalence of depression was 20.60% (n=71). From the total sample (n=345), 17.70% (n=61) had minimal depression, 2.00% (n=7) had mild depression, 0.58% (n=2) had moderate depression while 0.29% (n=1) had severe depression (Figure 1). Most of the participants with depression were female (63%; n=45), though this gender difference was not statistically significant (p=0.354).

Figure 1: Grades of depression among study participants



On bivariate analysis, presence of hypertension and prolonged duration on ART had statistically significant associations with depression (Table 3). On multivariate logistic regression, a longer duration on antiretroviral therapy was protective against depression (aOR = 0.85, 95% CI [0.74, 0.98], p=0.02) whereas being co-morbid with hypertension increased the risk of depression (aOR = 5.20, 95% CI [1.52, 32.68], p=0.03) (Table 4).

Table 3: Association between socio demographic and clinical characteristics versus depression

Variable	Depression No. (%)	No depression No. (%)	P- value
Marital status			0.748
Single	21 (30)	58 (21)	
Married	36 (51)	169 (62)	
Separated	4 (6)	10 (4)	
Divorced	2 (3)	7 (3)	
Widowed	8 (11)	30 (11)	
Level of education			0.806
Primary	17 (24)	66 (24)	
Secondary	31 (44)	134 (49)	
Tertiary	18 (25)	56 (20)	
University	5 (7)	18 (7)	
Occupation			0.588
Unemployed	5 (7)	24 (9)	
Self employed	44 (62)	149 (54)	
Employed	22 (31)	98 (36)	
Student	0	3 (1)	
Smoker			0.401
Yes	1 (1)	9 (3)	
No	70 (99)	265 (97)	
Drink alcohol			0.372
Yes	5 (7)	29 (11)	
No	66 (93)	245 (89)	
Hypertensive			0.0075
Yes	2 (3)	43 (16)	
No	69 (97)	231 (84)	
Diabetic			0.204
Yes	1 (1)	13 (5)	
No	70 (99)	261 (95)	
CD4 count (mean)	435	470	0.506
Years living with HIV (mean)	6.45(3.47)	5.80 (4.61)	0.273
Years on ART (mean)	5.81 (3.34)	4.68 (3.49)	0.016

Table 4: Multivariate logistic regression model for predictors of depression

Variables	Coefficients		
	aOR	95% CI	P-value
Years on ART	0.85	0.74 – 0.98	0.02
Years with HIV	1.10	0.97 – 1.23	0.13
Hypertension	5.20	1.52 – 32.68	0.03

Discussion

This study has demonstrated that one in every five HIV infected participants on antiretroviral therapy had features of depression. Participants with comorbid hypertension had 5 fold higher risk of depression while prolonged duration on ART was protective.

The prevalence of depression in our study is lower than that found in some developed countries. A prevalence rate of 58% was found among Black Americans living with HIV (21), 50% in China (22), and 28.1% in France (23). Our prevalence rate however is within the range of prevalence rates from a meta-analysis on depression among HIV positive patients in sub Saharan Africa, that showed a pooled prevalence of 9-32% (17). However, conflicting reports on prevalence rates across different sub Saharan countries have been cited, with rates of up to 56% in Nigeria (24), 40% in Uganda (25), and 37% in South Africa (26).

The widely differing prevalence rates may partly be attributed to the wide range of study designs employed, participant characteristics, and screening tools used in different settings. Apart from the PHQ-9, various other instruments have been validated for use, including the Beck Depression Inventory Score (BDI), the Center for Epidemiologic Studies Depression Scale Score (CES-D), the Mini-International Neuropsychiatric Interview (MINI), as well as a sub-scale of the Hopkins Symptom Checklist. The PHQ-9 and CES-D have been validated for use in sub Saharan Africa (17).

In Nigeria for example, the screening tool employed was the PHQ-9 with a cut-off of >9 (24), in Uganda the CES-D was employed with a cut-off of ≥23 (25), the Hopkins Symptoms Checklist with a cut-off of 44 in South Africa (26), and the CES-D with a cut-off of 16 in the US (21).

Another factor that may explain the difference in prevalence rates of the various studies include variations in socio-demographic characteristics of the populations under study. Compared to the USA for example where a prevalence rate of 58% among Black Americans was found (21), our lower prevalence rate may partly be explained by the better social support structures found within sub Saharan African communities. Compared to Western countries, African communities are usually more tightly knit, with social support structures built not only from spousal and parental support, but also from extended family and the community at large (27). Moreover, strong social support in patients with chronic illnesses such as HIV has been shown to be protective against depression (28).

Although no statistically significant association was found between gender and risk of depression, majority of the patients with depression in our study were females. Various studies have found an association between female sex and risk of depression (29–31), with HIV positive females reported to have more severe depressive symptoms compared to their male counterparts (32). Reasons for a possible higher risk of depression among females include neurobiological sex differences, women's lower levels of education, financial dependence, and females being more sensitive to life events, criticism, and separation (29).

Our study found an association between the number of years on antiretroviral therapy and depression, with a longer duration on ART being protective against depression. Although neuropsychiatric adverse effects including depression have been documented in association with efavirenz (33), several studies have demonstrated a possible protective effect of ART on the risk of mental health illness (34,35). The protective effect of long-term ART seen in our study may be due to the associated reduction in viral load within the CNS, reducing the risk of HIV-associated brain injury that may contribute towards depressive symptoms (5–7). Additionally, the longer the duration of therapy, the better the chances of having optimized antiretroviral therapy regimens and doses.

Patients with comorbid hypertension had a five-fold higher risk of depression in this study. It has previously been shown that patients with HIV, especially those over the age of 50 years, will have an average of four to five comorbidities, including hypertension (36). These comorbidities portend an additional source of frustration among HIV positive patients, compounding their concerns regarding hypertension-related complications such as myocardial infarction and stroke (37). These frustrations and fears may also contribute towards the association between hypertension and depression elucidated in this study.

Our study had several strengths. It was conducted at a tertiary centre with a diverse pool of patients representing various socioeconomic strata, educational levels, and communities, thus is a representative sample of an urban and periurban HIV positive patient cohort. Additionally, we used a depression screening tool that had undergone validation within a local culture and context (20).

Study limitations: This cross-sectional study design employed, by its very nature, does not in any way imply causality between HIV and depression. Additionally, the study was not powered to detect association between various antiretroviral regimens and depression, which would have provided important information to healthcare providers regarding regimens that may or may not be protective against depression in this lower middle income country setting. Nonetheless, we were able to demonstrate a relatively high prevalence of depression among HIV positive patients on HAART in a tertiary HIV clinic within sub-Saharan Africa. Additionally, we demonstrated a possible protective effect of long term HAART, and an association between comorbid hypertension and depression.

Conclusion and recommendations

The high prevalence of depression among HIV positive patients on ART highlights the need to integrate routine depression screening measures into HIV clinic care packages within sub Saharan Africa. In addition, we recommend extensive studies to correlate antiretroviral regimens, serum antiretroviral drug concentrations and adverse drug reactions with depressive illnesses among HIV infected patients on HAART.

Data availability: Datasets used are available on request (email: *george.mugendi@uonbi.ac.ke*).

Consent: Informed written consent was obtained from each participant prior to recruitment into the study.

Conflicts of interest: The authors declare no conflicts of interest.

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Original paper

Adherence to Immunosuppressive Therapy among Renal Transplant Recipients at Kenyatta National Hospital

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Abstract

Background: Renal transplant is the treatment of choice in end stage renal disease. Key in maintaining graft survival is use of immunosuppressive therapy as prescribed by the KDIGO guidelines

Aim: The primary objectives were to determine the proportion of Kidney Transplant Recipients (KTRs) adherent to immunosuppressant therapy and the relationship between adherence and graft function. The secondary objective was to identify the factors barring adherence to immunosuppressant therapy (IST).

Design: A cross-sectional descriptive study.

Setting: Kenyatta National Hospital (KNH).

Methods: The KTR was weighed in kilograms and a blood sample was then taken for serum creatinine level to calculate the estimated Glomerular Filtration Rate (eGFR) using the Cockcroft-Gault formula as a marker of graft function. Simplified Medication Adherence Questionnaire (SMAQ) was filled in by the patients or caregiver to assess for adherence.

Statistics: Statistical analysis was performed in SPSS version 21.0 software. Proportion of adherence to immunosuppressants was presented as percentages with 95% Confidence Intervals (CIs). Factors influencing adherence to immunosuppressants was tested using chi square test for categorical variables and independent t test to compare means. A multivariate analysis was done to assess for factors independently associated with adherence.

Results: A total of 106 KTRs were recruited between January and April 2018. Seventy point eight percent of kidney transplant recipients were adherent and there was a positive relationship between adherence and graft function with adherent KTRs having a median eGFR of 79mL/mL/min/1.73m² whereas non-adherent KTRs had a median eGFR of 42 mL/min/1.73m² and this was statistically significant with a p-value of <0.001. Factors barring adherence to immunosuppressive therapy included: KTR young age at transplantation, employment status, shorter duration of dialysis pre-transplantation and pill count.

Conclusion: Adherence in our population was comparable to other centers in the world at 70.8% but we still have room for improvement of adherence addressing factors identified.

Key words: Adherence, Kidney Transplant Recipients (KTRs), Questionnaire and factors barring adherence

Introduction

Over the years, renal transplantation has been deemed the treatment of choice in end stage kidney disease rather than haemodialysis. Immunosuppressive therapy is the mainstay in the maintenance of renal allografts. To avoid organ rejection, which is a major cause of transplant failure, one has to be adherent to the immunosuppressive therapy as prescribed. Adherence to therapy is defined as the extent to which a patient follows the instructions of the health care provider with regard to taking medications and adopting a healthy lifestyle. Non-adherence to Immunosuppressant Therapy (IST) is a recognized predictor of negative medical outcomes after solid organ transplantation (1). Poor adherence to immunosuppressant therapy in kidney recipients contributes to an estimated 20% of acute rejections and 16% of graft losses (2).

Studies across the world have put adherence to IST among KTRs between 24% (3) and 73.6% (4) and have been able to identify barriers to adherence. These barriers include mental disorders such as depression or anxiety (5), young KTR aged 18 – 29 years (6), male gender (7), married KTRs in unhappy marriages (8), low education level (3), lower income status (9), occupation status (8), longer duration since transplantation (7,10), frequency and number drugs (7,11) and cost of drugs (12). Adherence impacts both graft and patient survival due to the risks associated with graft failure. Methods used in assessing adherence to ISTs in KTRs include: direct pill count, laboratory drug level monitoring, electronic pill box monitoring or self-reported questionnaires.

Graft function can be used using different methods including: serum creatinine level, creatinine clearance, estimated Glomerular Filtration Rate (eGFR) or renal scintigraphy. Assessment of adherence is important

in KTRs and we have no data out of Kenya or Africa showing the rates. Identification of barriers is also important to allow for early intervention.

The main aim of this study was to find out the proportion of adherent KTRs at KNH, to demonstrate the relationship between adherence and graft function and to delineate factors barring adherence.

Materials and methods

The study design was a hospital based descriptive cross sectional study carried out at the outpatient Renal Transplant Clinic at the Kenyatta National Hospital. The Transplant Clinic runs every Tuesday and an average of 15 – 20 patients are seen at every clinic.

Case definition was any consenting/assenting individual above the age of 13 years 3 months post-transplant attending the KNH Transplant Clinic. Using the formula for a finite population, the minimal sample size calculated was 102 KTRs. We did consecutive sampling of all patients attending the Transplant Clinic.

Data collection involved the use of a structured study proforma to obtain demographic and clinical characteristics of KTRs. The principal investigator (PI) and a research assistant then weighed the patient using a standardized scale in kilograms and drew a 3mls blood sample for serum creatinine level. SMAQ, a self-administered questionnaire was then given to the KTR to fill in as truthfully as possible.

Dependent variables were eGFR and where patient was adherent or not. Independent variables included: age, gender, marital status, education level, employment status, mode of payment for post-transplant care, duration of dialysis pre-transplantation, duration since transplantation and number of medication currently in use.

The first 4 questions on the SMAQ questionnaire have a yes/no answering system while question 5 asks the patient to pick one answer that best suits him in an option of 5 answers. Question 6 is an open ended question with the patient required to indicate the number of days of missed medication. A patient was classified as non-adherent if he/she responds to any of the first 4 questions with a non-adherent answer, and in terms of quantification, if the patient lost more than two doses during the last week or had not taken medication for more than two complete days during the last three months. The questionnaire only applied to IST and not to other drugs in use.

Statistical analysis was performed in SPSS version 21.0 software. Proportion of adherence to ISTs was presented as percentages with 95% Confidence Intervals (CIs). Factors influencing adherence to ISTs were tested using chi square test for categorical variables and independent t test to compare means. Multivariate analysis for factors independently associated with adherence was done.

Initiation of the study was carried out after a written approval was issued by the Department of Clinical Medicine and Therapeutics as well as the KNH/ UoN Ethics and Research committee.

Results

Between 3rd January 2018 and 30th April 2018, 109 KTRs were interviewed at the KNH Renal Transplant Clinic. Two declined consent while one was too unwell to give consent. One hundred and six KTRs were thus recruited fulfilling the required minimal sample size of 102 participants.

Study participants characteristics: The mean age of study participants was 44.3 years with age ranging from 26 years to 67 years. Sixty six percent of the KTRs were male and 76.4% of KTRs were married. Sixty three point two percent of KTRs were employed of whom 15.1% were self-employed. Majority of KTRs were paying for post-transplant care in cash at 81.1%. Eighty five point seven percent of KTRs had post-primary education. The top 3 counties of residence were Nairobi county at 23.6%, Kiambu county at 14.1% and Murang'a county at 10.3%. These study participant characteristics are summarized in Table 1.

The clinical characteristics of the study participants are summarized in Table 2. The top causes of end stage renal failure in these KTRs were hypertension at 46.2%, chronic glomerulonephritis (The top causes of end stage renal failure as documented in the file were hypertension at 46.2%, Chronic Glomerulonephritis (CGN) at 34% and Diabetes Mellitus (DM) at 22.6%.
All KTRs had undergone dialysis and had a median dialysis duration of 18 months with a range of 3 months to 108 months (9 years). Of note there were 5 KTR patients in the study who were on ongoing dialysis due to failed grafts. Duration since transplantation had a median duration of 54 months with a range of 3 months to 302 months (25 years).104 (98.1%) KTRs had only one renal grafting done while 2 KTRs (1.9%) had a second renal transplant done.

Table 1: Study participant demographic characteristics

Variable	Frequency (%)
Mean age (SD)	44.3 (11.3)
Sex	
Male	70 (66.0)
Female	36 (34.0)
Marital Status	
Single	22 (20.8)
Married	81 (76.4)
Widowed	2 (1.9)
Separated	1 (0.9)
Employment status	
Employed	51 (48.1)
Unemployed	28 (26.4)
Retired	11 (10.4)
Self employed	16 (15.1)
Education level	
None	1 (1.0)
Primary	14 (13.3)
Secondary	44 (41.9)
Tertiary	46 (43.8)
Medical cover	
NHIF	4 (3.8)
Private insurance	3 (2.8)
Employee scheme	13 (12.3)
Cash	86 (81.1)
County of residence	
Nairobi County	23.6%
Kiambu County	14.1%
Murang'a County	10.3%
Nakuru	5.6%
Nyeri	5.6%
Embu	4.72%
Nyahururu	3.77%
Others	32.31%

In patients with functioning grafts, the median creatinine level was 111.5µmol/L (IQR of 92 – 175µmol/L) with an eGFR median of 71.5mL/min (IQR of 46.5 – 88.5mL/min). Those with failed grafts and undergoing dialysis had a median creatinine level of 448µmol/L (IQR of 374 – 860 µmol/L) with an eGFR median of 12.5mL/min (IQR 9 – 16mL/min).

Table 2: Clinical characteristics of participants

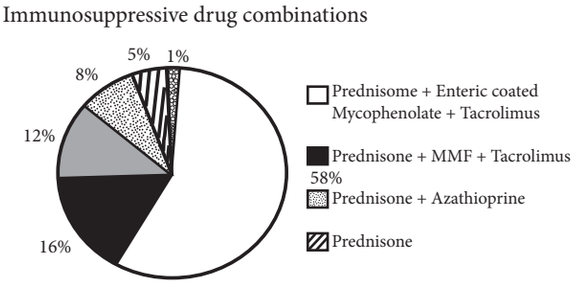
Variable	Frequency (%)
Cause of end stage renal failure	
Chronic glomerulonephritis	36 (34.0)
Diabetes nephropathy	24 (22.6)
Hypertensive renal disease	49 (46.2)
Obstructive uropathy	2 (1.9)
Polycystic kidney disease	1 (0.9)
Chemotherapy Induced	1 (0.9)
Eclampsia	6 (5.7)
Gout	1 (0.9)
SLE	1 (0.9)
Dialysis duration pre-transplantation (months)	
1-12	39 (36.8)
13-24	32 (30.2)
25-36	19 (17.9)
> 36	16 (15.1)
Duration since transplantation (months)	
1-12	7 (6.6)
13-24	10 (9.4)
25-36	27 (25.5)
> 36	62 (58.5)
Previous renal graft	
None	104 (98.1)
One	2 (1.9)
Mean weight (SD) in Kg	73.2 (+/-13.9)
Median creatinine (IQR) in functioning graft	111.5 (92.0-175.0)
Median eGFR (IQR) in functioning graft	71.5 (46.5-88.5)
Median creatinine (IQR) in failed graft	448 (374 – 860)
Median eGFR (IQR) in failed graft	12.5 (9 – 16)

The medication used by study participants was summarized in Table 3. All KTRs were on prednisone. The most commonly used calcineurin inhibitor (CNI) was tacrolimus at 75.5% and anti-proliferative agent was enteric coated mycophenolate sodium at 74.5%. Total pills used by KTRs had a median value of 11 with a range of 5 – 16.

Table 3: Medication used by KTRs

Variable	Frequency (%)
Immunosuppressant therapy	
Prednisone	106 (100.0)
Mycophenolate mofetil	12 (11.3)
Mycophenolate sodium	79 (74.5)
Cyclosporine	17 (16.0)
Tacrolimus	80 (75.5)
Sirolimus	1 (0.9)
Azathioprine	9 (8.5)
Concomitant medication use	
Antihypertensives	80.2%
Hypoglycemics	31.1%
Statins	11.3%
Others	22.2%

Figure 1: Pie chart of IST combinations



Adherence to immunosuppressant therapy: The proportion of KTRs adherent to ISTs was 70.8% (CI 61.3 – 79.2) as determined by use of the SMAQ questionnaire. This was an absolute finding on whether adherent or not.

Comparison between adherent and non-adherent KTRs: Comparison between adherent and non-adherent KTRs characteristics are summarized in Table 4. The mean age of the adherent population was 46.4 years compared to the non-adherent group who had a mean age of 38.9 years and this was statistically significant with a p-value of 0.002. Ninety point nine percent of retired KTRs were adherent which was statistically significant with a p-value of 0.033 (OR of 8.7 CI of 1.0 – 77.1) compared to 87.5% of self-employed KTRs nearing significance with a p-value of 0.053 (OR of 2.1 CI of 0.8 – 5.4), 70.6% of employed KTRs and 53.6% of unemployed KTRs. Ninety four point seven percent of KTRs who dialyzed for 25 – 36 months and 87.5% of KTRs who dialyzed for more than 3 years were adherent and both were statistically significant with a p-values of 0.015 and 0.04 respectively (OR 13.9 CI 1.7 – 114.8 and 5.4 CI 1.1 – 27.1 respectively) compared to 65.5% of KTRS who dialyzed for 13 – 24 months and 56.4% of KTRs who dialyzed for less than a year being adherent. Though significant, the confidence interval was wide looking at duration of dialysis of 25 – 36 months and the instability was due to the small numbers in this study but still significant as it did not touch nor cross the null value.

Adherent KTRs had a higher pill burden with a median of 9 while non-adherent KTRs had a median pill count of 8 and this was statistically significant with a p-value of 0.037. Adherent KTRS had a median eGFR of 79 mL/min/1.73m² (IQR 69 – 95 mL/min/1.73m while non-adherent KTRs had a median eGFR of 42 mL/min/1.73m² with an IQR of 26 – 49 mL/min/1.73m² and this was statistically significant with a p-value <0.001. This distribution is demonstrated by the box and whisker plot in Figure 2.

Figure 2: Box and whisker plot comparing graft function in adherent vs non-adherent

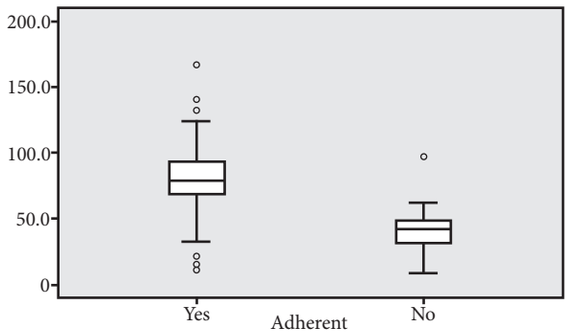


Table 4: Comparison between adherent and non-adherent KTRs to ISTs

Variable	Adherent (%)	Non-adherent (%)	OR (95% CI)	P-value
Mean age (SD)	46.4 (11.9)	38.9 (7.4)	-	0.002
Sex				
Male	46 (65.7)	24 (34.3)	2.2 (0.8-5.7)	0.116
Female	29 (80.6)	7 (19.4)	1.0	
Marital status				
Not married	14 (56.0)	11 (44.0)	0.4 (0.2-1.1)	0.068
Married	61 (75.3)	20 (24.7)	1.0	
Employment status				
Unemployed	15 (53.6)	13 (46.4)	1.0	
Employed	36 (70.6)	15 (29.4)	2.1 (0.8-5.4)	0.133
Retired	10 (90.9)	1 (9.1)	8.7 (1.0-77.1)	0.033
Self employed	14 (87.5)	2 (12.5)	6.1 (1.2-31.8)	0.053
Education level				
None	1 (100.0)	0	-	1.000
Primary	9 (64.3)	5 (35.7)	1.0	
Secondary	32 (72.7)	12 (27.3)	1.5 (0.4-5.3)	0.547
Tertiary	33 (71.7)	13 (28.3)	1.4 (0.4-5.0)	0.595
Mode of care payment				
Insurance	17 (85.0)	3 (15.0)	2.7 (0.7-10.1)	0.131
Cash	58 (67.4)	28 (32.6)	1.0	
Dialysis duration pre-transplantation (months)				
1-12	22 (56.4)	17 (43.6)	1.0	0.430
13-24	21 (65.6)	11 (34.4)	1.5 (0.6-3.9)	0.015
25-36	18 (94.7)	1 (5.3)	13.9 (1.7-114.8)	0.040
> 36	14 (87.5)	2 (12.5)	5.4 (1.1-27.1)	
Duration since transplantation (months)				
1-12	7 (100.0)	0	-	
13-24	7 (70.0)	3 (30.0)	0.8 (0.2-3.3)	0.999
25-36	14 (51.9)	13 (48.1)	0.3 (0.1-0.9)	0.695
> 36	47 (75.8)	15 (24.2)	1.0	0.028
Pill burden, median (IQR)	9 (7-10)	8 (6-9)	-	0.037
Median creatine (IQR)	102 (85-115)	194 (174-221)	-	<0.001
Median eGFR (IQR)	79 (69-95)	42 (26-49)	-	<0.001

Discussion

This study was done to assess what proportion of Kidney Transplant Recipients (KTRs) were adherent to Immunosuppressant Therapy (IST) and further delineate factors baring adherence. Our KTR population consists of young, male, married individuals with majority having post-primary education and employed. This is important as they are a key work force population and drive the economy thus requiring good health to take part in daily activities.

Seventy point eight percent of KTRs were adherent to ISTs which is comparable to Chisholm-Burns *et al's* (6) study from Arizona, USA who showed that 65.5% of KTRs were adherent and that of Massey *et al* (10) from Rotterdam, Netherlands at 73% of KTRs adherent. The aforementioned studies both used questionnaire based tools for assessment of adherence and had similar patient population with the main difference being that Chisholm-Burns study population had majority with medical insurance cover and both had a majority Caucasian population. The proportion of adherent KTRs was higher than a study done by Griva *et al* (8) at 58.6% where they used a self-reported questionnaire along with blood drug level monitoring and Obi *et al* (7) at 61.5% who used serum drug level only. This could be attributed to the fact that serum drug assay is more sensitive compared to questionnaire based adherence evaluation and is less prone to manipulation by study respondents

who might not answer the questionnaire truthfully to avoid detection of non-adherence. Though drug level monitoring is more sensitive in eliciting adherence, we didn't use it as it was limited by unavailability of assays for other ISTs such as prednisone or azathioprine as well as inability to delineate causes of non-adherence. Twenty nine point two percent of KTRs were non-adherent and this is significant as we only use living related donors in our setting thus exposing a healthy population to the risks associated with donation. There were no studies published out of Africa for local comparison on adherence to ISTs.

Graft function in KTRs was significantly impacted by adherence to ISTs. This was in keeping with Butler *et al* (13) who demonstrated in a meta-analysis that the odds of graft failure were seven fold in non-adherent KTRs compared to adherent KTRs. This meta-analysis included both cross-sectional and cohort studies as well as studies that used self-reported adherence questionnaires and electronic monitoring. Thus, though the findings were comparable to our study, there was a difference in methodology. Though our study found a significant positive relationship between adherence and graft function, this study wasn't powered enough to make a correlation or have a predictive value due to the small study population.

Factors baring adherence have been studied in other centers and commonly identified factors include young age, (6) male gender, (7) marital status, (8) longer duration since transplantation (7,10) and pill burden (7,11).

Adherent KTRs had a mean age of 46.4 years compared to non-adherent KTRs who had a mean age of 38.6 years. This was similar to a study by Chisholm-Burns *et al* (6) who demonstrated that patients in the age group of 46 – 64 years showed highest adherence rate while those aged 18 – 29 years had least adherence and also made use of a self-reported questionnaire. The similarities in methodology in terms of a questionnaire based tool use and cross-sectional sampling with this study further lent credence to this finding. Young KTRs especially adolescents have a negative belief in medication and thus were more non-adherent (14). Social support including use of support groups and post-transplant counseling was used by Chisholm-Burns *et al* (15) to improve in adherence especially in the young adult population who were more prone to non-adherence.

Ninety point nine percent of retired KTRs were significantly adherent compared to other groups. These KTRs were older and had undergone dialysis for a longer duration both of which had positive significant findings in terms of adherence. Additionally, these individuals had more free time to attend clinic, source medication and follow instruction while also having the financial capacity as majority were under a pension scheme that provided health benefits.

Duration of dialysis pre-transplantation also showed a difference across the various groups. Highest adherence rate was in patients who had undergone dialysis for 25 – 36 months with an adherence rate of 94.7% and lowest adherence in the group that dialyzed less than 1 year with only 56.4% adherent. We attributed this to the degree of preparation and counseling pre-transplant which is usually carried out at the pre-transplant clinic. Those who were transplanted very quickly had less time for counseling and education and were more likely to be non- adherent. We also postulated that patients who had undergone longer dialysis sessions valued their grafts more due to prior recurrent hospital visits for dialysis and protracted hospitalization due to renal failure associated complications and had prior poor quality of life as demonstrated by Kamau *et al* (16) and thus guarded their grafts more. On multivariate analysis, duration pre-transplantation was the only factor independently associated with adherence and thus was the most significant finding of this study.

Duration since transplantation though not having any significant findings demonstrated a clear pattern of a drop in adherence as time progressed from those with a duration of less than 12 months at 100% adherent to the lowest in those with a duration of 25 – 36 months after transplantation at 51.9% adherent and picking up once more after 36 months to 75.8%. This showed a gap in adherence follow up post-transplantation and raised the need of post-transplantation counseling and assessment which is currently not done.

Adherent KTRs had a higher pill count than non-adherent KTRs and this was in contrast to Obi *et al* (7) who showed that a reduced pill count improved adherence and Adhikari *et al* (11) who showed that pill count does not impact on adherence. These two studies both used self-reported questionnaires to assess adherence but differed in that Obi *et al* (7) carried out a cross-sectional study and focused only on tacrolimus adherence while Adhikari *et al* (11) did a longitudinal study looking at total IST pill count. These differences in study methodology may explain the difference in findings. We attributed our findings to the fact KTRs in our population with a higher pill count were mostly composed by those with a shorter duration since transplantation and thus their prescriptions had higher doses of immunosuppressant therapy hence a higher pill count as well as some were on anti-microbial prophylaxis in addition to ISTs and medication for other comorbidities. This same group though showed a higher adherence rate as earlier described by Massey *et al* (10) in patients with a shorter duration since transplant. Whereas, patients with a longer duration since transplant had their pill count reduced as they were at the minimum required dose to achieve immunosuppression as recommended

by the KDIGO guidelines (17) and further included the group of patients with failed grafts who were only on 5mg once a day of prednisone for immunosuppression and off other ISTs hence a lower pill count.

Conclusions

The proportion of adherent KTRs to IST was at 70.8%. There is a positive relationship between adherence and graft function in our KTRs. Factors barring adherence to ISTs in our settings are;

(i) Young age
(ii) Employment status
(iii) Duration of dialysis pre-transplantation
(iv) Duration since transplantation
(v) Pill burden

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Original paper

Promoting Patient-Centered Care – a Continuous Quality Improvement (CQI) Initiative Utilizing the Plan-Do-Study-Act (PDSA) Cycle at a HIV Care Clinic in Kenya

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Abstract

Introduction: An estimated 5% of persons living with HIV (PLHIV) in Kenya reside in Kiambu County. This huge caseload presents a challenge to service delivery within the context of strained health systems. Patient centered models of care are increasingly being mooted as a way to improve client satisfaction with health care, improve efficiency and to decongest health facilities.

Objective: The study sought to explore whether a Continuous Quality Improvement (CQI) intervention utilizing the Plan-Do-Study-Act (PDSA) cycle would help minimize service delays at a Level 5 facility in Kiambu County.

Methods: A baseline time-motion study was undertaken amongst conveniently sampled subjects (n=201) attending the Kiambu Level 5 HIV care clinic between 11th and 15th February 2013. Study subjects had a time stamp inserted onto their study record at every service point documenting the time of service commencement and termination. Data were summarized in a spreadsheet and mean service duration and waiting times computed. A 'package of change' was then formulated and a repeat time-motion study undertaken 12 months later. The Student's t-test was used to compare mean service and waiting times between the baseline and follow-up populations.

Results: A total of 201 and 176 subjects took part in the baseline and follow-up studies respectively. There were more males (30.4%) in the follow-up study compared to the baseline study (26%). The mean age of participants was 35.1 years in the baseline study and 36.5 years in the follow-up study. For the baseline population, mean service duration times were as follows: Registration 12min, Triage 2.5min, Doctor 10.5min, Pharmacy 5.5min. Waiting times were: Post-registration 50min, post-triage 70min and post-consultation 61min. On analysis of service duration and waiting times in the follow-up population, there was a significant reduction of waiting time between consultation and pharmacy (-27.5 min, CI: -36.0, -19.0, $p<0.00006$) and reduced pharmacy dispensing time (2.2 min, CI:-3.55, -0.93, $p<0.0008$).

Discussion: The study highlights the application of PDSA in addressing common challenges to delivery of patient centered care in the context of chronic illnesses. The following steps were undertaken sequentially: problem definition, quantification of the problem utilizing a baseline time motion study, root cause analysis and formulation of a "change package". Evaluation of the impact of the change was then conducted through a repeat time motion study 12 months later. A comparison of follow-up findings against baseline findings enabled identification of other factors contributing to service delays – which were then prioritized for action in the next PDSA cycle.

Conclusion: This study vindicates the use of a PDSA approach in effecting Small Tests of Change (STOC) aimed at achieving optimal patient centered care.

Key words: Client-centred care, Quality improvement, PDSA cycle, HIV, Waiting time

Introduction

The World Health Organization (WHO) recognizes service delivery as one of six core health systems building blocks (1). Consequently, the adoption of patient-centered models of care is on the increase (2). Health services are deemed 'good' when they 'deliver effective, safe and quality interventions to those that need them, when and where needed.' (2). The Institute of Medicine defines patient-centered care as 'healthcare that establishes a partnership among practitioners, patients and their families… to ensure that decisions respect patients' wants, needs, and preferences and that patients have the education and

support they need to make decisions and participate in their own care' (3). Patient-centered care improves patients' satisfaction with services and efficiency of service utilization (4). With an estimated 1.6 million Persons Living with HIV (PLHIV), Kenya is among the top four HIV 'high burden' countries in Africa (5). This enormous workload against a backdrop of weak and inequitable health systems may in part explain why patient-centered care remains an elusive goal (6-9).

An estimated 5% of Kenyans living with HIV reside in Kiambu County - which ranks 6th nationally in terms of absolute caseload (10). While scale up of Antiretroviral Therapy (ART) has significantly improved life expectancy (11), the challenge of providing chronic longitudinal care to PLHIV is still apparent in crowded waiting bays and long queues. Between 2011 and 2016, in partnership with the United States-Centers for Disease Control and Prevention (CDC), and the Ministry of Health (MOH) Kenya, the University of Nairobi CRISS Project (Central Kenya response: Integration strengthening and sustainability project) provided critical health systems support for HIV service delivery in Kiambu County - under the US President's fund for emergency AIDS relief (PEPFAR). To begin to understand reasons for service delays as a prelude towards developing a patient centered care model, the team adopted a Continuous Quality Improvement (CQI) approach using the Plan-Do-Study-Act cycle (PDSA) (12-14).

Materials and methods

Following the findings of a patient survey that revealed sub-optimal levels of satisfaction with HIV services, the CQI team identified long waiting times as a key area of concern. We therefore undertook a baseline time-motion study amongst conveniently sampled subjects (n=201) attending the HIV care clinic between 11th and 15th February 2013. In summary, verbally consenting subjects had a pre-tested study time-sheet on which every service provider recorded the time service began and ended. Data were summarized in a spreadsheet and mean service duration and waiting times computed. Preliminary analysis of waiting times against case-load suggested that service delays might have other contributory factors. Following a consultative meeting between the CQI team and facility staff, a 'package of change' was formulated. A repeat time-motion study was undertaken after 12 months. To determine the one year impact of changes to standard practice, the Student's t-test was used to compare mean service and waiting times between the baseline and follow-up populations.

Results

For a period of five days in February 2013 (Baseline) and nine days in February 2014 (Follow-up), consenting subjects participated in a time-motion study. Demographic characteristics for the two groups are shown in Table 1. For the baseline population, waiting times were compared to case-loads in the preliminary analysis (Figure 1 and Table 2).

Table 1: Demographic profiles of study subjects

Characteristic	Baseline study	Follow-up study
Total clients, n	201	176
Males, %	26%	30.4%
Mean age, years. (SD)	35.1(12.1)	36.5(11.1)
Median age, years.	35	37
Range age, years.	1.5-75	5-61

Figure 1: Waiting time vs. case load for the baseline population

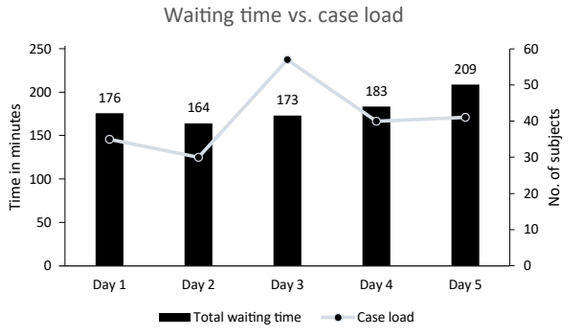


Table 2: Correlation coefficient – Waiting time vs. case loads

		Waiting time	Case load
Waiting time	Pearson correlation	1	*0.125*
	Sig (2-tailed)		0.841
	N	5	5
Case load	Pearson correlation	*0.125*	1
	Sig (2-tailed)	0.841	
	N	5	5

Average service and waiting times for the baseline and follow-up study populations were computed and summarized (Figures 2 and 3).

Figure 2: Mean clinic service and waiting times – Baseline population (2013)

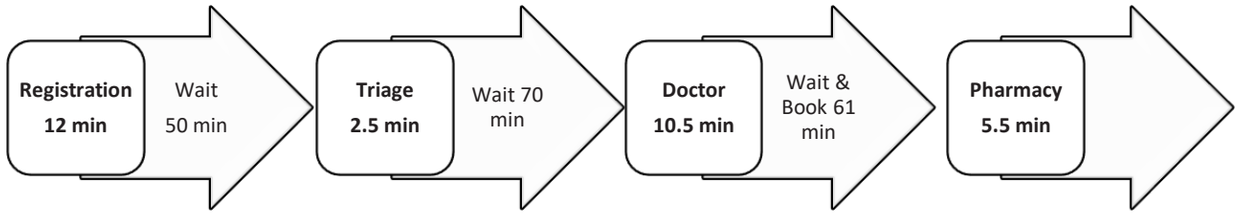
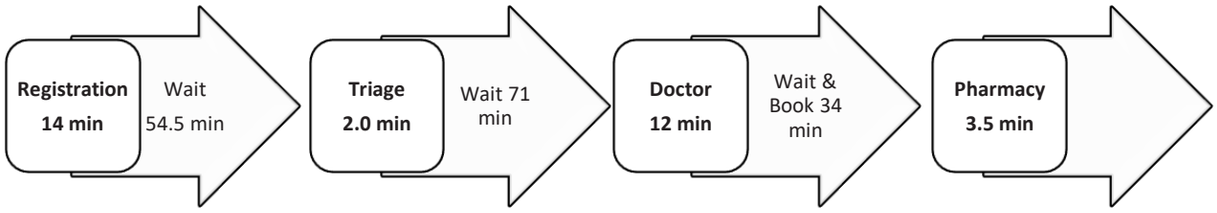


Figure 3: Mean clinic service and waiting times – Follow-up population (2014)



Detailed analyses of service duration and waiting times are summarized in Tables 3 and 4.

Table 3: Service duration time at key service delivery points

	Registration		Triage		Consultation		Pharmacy	
	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline
Observations, n	198	184	186	185	196	152	178	192
Mean (SD) Duration (min)	14.03 (16.62)	12.10 (10.49)	2.04 (1.51)	2.58 (2.92)	12.09 (14.63)	10.40 (8.81)	3.48 (3.08)	5.72 (8.75)
Difference in means(95% CI)	1.93 (-0.83 to 4.70)		-0.54 (-1.01 to -0.07))		1.69 (-0.80 to 4.18)		-2.24 (-3.55 to -0.93)	
P value	*0.171*		*0.0244*		*0.184*		*0.0008*	

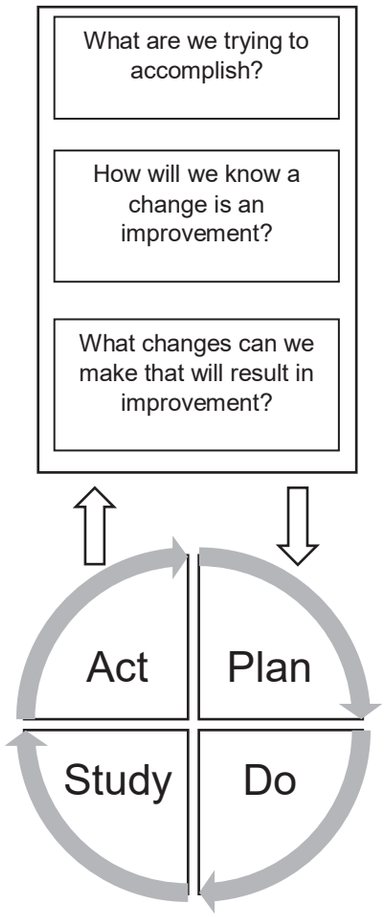
Table 4: Waiting time in-between services

	Registration to Triage		Triage to Consultation		Consultation to Pharmacy	
	Follow-up	Baseline	Follow-up	Baseline	Follow-up	Baseline
Observations, n	176	175	180	142	169	128
Mean (SD) Duration (min)	54.5 (32.83)	51.30 (29.00)	70.92 (44.86)	67.58 (34.17)	32.72 (37.2)	60.21 (37.18)
Difference in means(95% CI)	3.20 (-3.28 to 9.69)		3.34 (-5.28 to 11.97)		-27.49 (-36.04 to -18.95)	
P value	0.332		0.4472		<0.00006	

Discussion

This study highlights the application of the PDSA cycle (Figure 4)(15) in effecting meaningful change towards improving the care experience for patients with chronic illness.

Figure 4: PDSA cycle



** adopted from ACT academy, NHS improvement*

The first step was to define the problem, in this case, low scores on a recent patient satisfaction survey. Insight from further probing revealed that long waiting periods were the most frequent cause of dissatisfaction with clinic services, an observation reported in other African countries (16,17). To quantify the magnitude of the problem, the CQI team consultatively undertook a baseline time-motion (patient-flow) study which suggested that case-work load alone could not account for service delays (R=0.125, *p - 0.841*). Root cause analysis identified inadequate staffing and poor triage practice as prime target areas for intervention (Plan). Over the next 12 months, the 'change package' comprising automated triage equipment, Continuous Medical Education (CMEs) on effective triage augmented by continuous mentorship and additional staff (1 triage nurse, 2 clinicians and 1 pharmaceutical technologist) was rolled out - (*Do*). To study the effect of this Small Test Of Change (STOC) (18), a repeat time-motion study was done. There was very strong evidence to suggest that the 'package of change' was associated with reduced waiting time between the consultation and pharmacy ($p<0.00006$) and reduced pharmacy service time ($p=0.0008$). Further, there was moderately strong evidence for improvement in triage service time ($p=0.0244$). Following a series of brainstorming sessions between the CRISS Project team and facility staff, it was hypothesized that despite the deployment of two additional clinicians, triage-to-consultation and consultation times did not improve primarily due to infrastructural constraints. Additionally, non-scheduled visits (first come-first served basis) were flagged out as a potential contributor to slow registration and prolonged pre-triage times – an observation confirmed by a later study at the same facility where the registration department was the commonest source of delay (19).

Consequently, redesign of clinic space and appointment scheduling were prioritized for implementation at the HIV clinic (ACT) and this 'modified package of change' proposed for roll out at project sites with similar characteristics – (Plan for next cycle). It is important to point out that PDSA cycles are iterative and that many cycles may run sequentially if study results reveal different approaches are necessary or simultaneously if desired objectives involve different parts of the whole.

Conclusion

This study focused on service delays as a CQI problem and the use of a PDSA cycle to develop patient centered solutions. Instructively, our modified change package, though focused on service delivery, required the input of other essential blocks - Human Resources for Health (HRH), information, financing, leadership and technology. Indeed a 'whole of system approach' is often needed to effect and sustain meaningful change due to the 'inter-dependence' of the different components of the framework (1,20). Models of care, such as the chronic care model (21), that are centered on Picker's eight principles, contribute to health system goals of effectiveness and efficiency (22,23). Our project is currently implementing a differentiated-care model to decongest clinics, improve patient satisfaction and accelerate progress towards achievement of the 90-90-90 strategy (24,25). Our study vindicates the use of a PDSA approach in effecting Small Tests Of Change (STOC) aimed at achieving optimal patient centered care.

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To Kiambu level 5 Hospital CCC team.

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Review paper

Treatment Approaches for Multiple Myeloma: A Review

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Abstract

Background: Multiple Myeloma (MM) is a haematological cancer characterized by complications of end-organ damage and subsequently high mortality. Previously, there were few therapies available with minimal survival benefit for most patients. Survival was less than a year in many countries. The survival of MM patients can range from 6 months to over 10 years, with a median of 6 years, depending on stage of the disease at diagnosis and prognostic factors. However, with the advent of newer immune modulating agents and novel therapies, there exists an opportunity to improve the management of MM.

Objective: The purpose of this review is to discuss the current chemotherapy and novel agents available for treatment of Multiple Myeloma and highlight emerging therapies in treatment of Multiple Myeloma, some of which are now locally available in Kenya.

Data Sources: International Guidelines on Treatment of Multiple Myeloma; Published articles from peer-reviewed journals; ESMO, NCCN guidelines on Multiple Myeloma

Conclusion: New MM therapies have been shown to improve progression-free survival and overall survival of to upto 82% at four years. Some of these therapies are now accessible locally through government funding. In combination with a wholesome approach which includes appropriate supportive care, there exists an opportunity to improve the quality and standard of care of MM patients in Kenya to replicate the success of that in developed countries.

Key words: Multiple myeloma, Cancer

Introduction

Multiple Myeloma (MM) is a chronic B-cell malignancy that involves proliferation of neoplastic clonal plasma cell in the bone marrow with subsequent overproduction of monoclonal immunoglobulins or its constituent polypeptide chains in serum and urine (paraproteins). According to the World Health Organisation (WHO), MM is recognized as a disease distinct from other plasma cell disorders such as Monoclonal Gammopathy of Uncertain Significance (MGUS), solitary plasmacytoma of bone, systemic light-chain amyloidosis and POEMS (polyneuropathy, endocrinopathy, monoclonal plasma cells disease and skin changes) syndrome (1). MM derives its distinctness from other plasma cell disorders by the manifestation of characteristic clinical symptoms from end-organ damage including renal dysfunction, anaemia, extensive skeletal lytic lesions and hypercalcemia caused by the pathophysiological effects of the circulating abnormal paraproteins.

Epidemiology

Multiple Myeloma (MM) is a cancer, with a lifetime risk of 0.76% (2) and an age-adjusted incidence rate of 2.5-7.2 per 100,000 in Western countries (3). Globally, cases of MM have increased by 126% from 1990 to 2016, with older age contributing to more than half of the rise in cases (4). The reported incidence rate is low in sub Saharan Africa but noted to be on the rise following improved diagnostic capabilities and increased life expectancy (4). There is no local prevalence data available for (MM) in Kenya in the Kenya cancer registry (5a Population-Based Cancer Registry (PBCR) or other East African registries (6). In the West, it is considered a disease of the elderly, affecting those in their 7^{th}-8^{th} decades, with African American/blacks being two-three times more likely to be affected (7). However, in Kenya, one previous study put the median age of presentation at 59 years of age (8), while another describes a majority of cases as occurring in the 6^{th}-7^{th} decade with a male : female ratio of 1.37:1 (9).

The survival of MM patients can range from 6 months to over 10 years, with a median of 6 years (10), depending on stage of the disease at diagnosis and prognostic factors (11). Despite improvements in treatment, MM is still characterized by frequent relapses and death due to disease progression, with MM accounting for approximately 19% of cancer mortality in the United States (12). The mortality rate in Europe stands at 13 and 20 per 100 000 in males and females respectively. However, the life expectancy of MM patients in Western countries has largely improved from less than one year in the 1960s (13) to 5 to 7 years in patients receiving current treatment modalities (14). Locally, the follow-up duration and survival have been described as short (9).

Treatment of multiple myeloma

The only cure for MM is allogeneic stem cell transplant. However, allogeneic transplant is associated with high incidences of treatment related mortality and graft versus host disease (15). A recent systematic review and meta-analysis found a lack of consistent survival benefit of allogeneic transplant in MM patients in standard risk patients as compared to Autologous Stem Cell Transplant (ASCT) due to high incidences of treatment related mortality at 44% (16). However, allogeneic stem cell transplant was suggested for young patients with high cytogenetic risk with a poor prognosis as the risk of disease progression is higher than that of the adverse effects from the transplant.

The universal gold standard for MM treatment is induction therapy followed by Autologous Stem Cell Transplant (ASCT) for eligible patients. ASCT prolongs progression-free survival and overall survival among patients and is recommended in patients under the age of 65 years with no substantial cardiac, lung, renal or hepatic dysfunction (17). Eligible patients are started on 3 to 4 cycles of induction therapy for 2 – 4 months followed by ASCT. After transplant, maintenance therapy with lenalidomide or bortezomib is recommended in most patients (Figure 1). ASCT has been shown to achieve 4 year overall survival rates of 82% patients under 65 years in the Intergroupe Francophone du Myelome (IFM) 2009 trial (18) and replicated in the real-world experience at the Mayo Clinic (19). ASCT with maintenance therapy, when compared to patients receiving chemotherapy with melphalan, prednisone and lenalidomide, had much higher 4-year overall survival rate, 81% compared to 65%, and a longer progression-free survival of 43 months compared to 22 months (17). However, ASCT is currently not available in sub Saharan Africa with the exception of South Africa (4). Chemotherapy is the common option for treatment given for MM for induction and maintenance therapy.

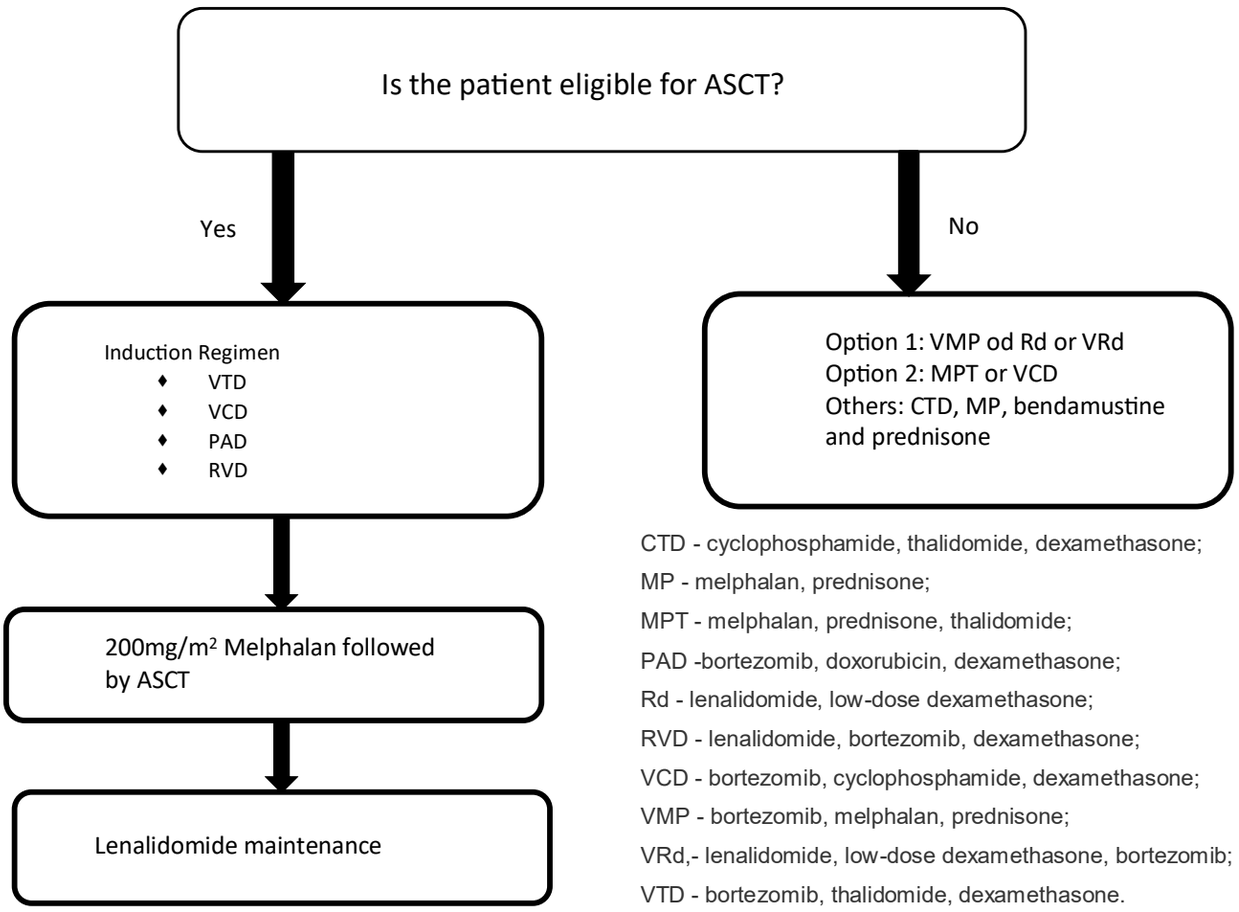
Table 1: Common therapeutic options in multiple myeloma

Drug class	Mechanism of action	Examples
Alkylating agents	Covalent linkage of alkly groups to DNA bases leads to crosslinking of DNA and inhibit further DNA transcription	Melphalan, Cyclophosphomide
Immunomodulatory Imide Drugs (IMIDS)	Reduce Tumour Necrotic Factor (TNF) and other cytokines, anti-angiogenesis and stimulate proliferation and activation of T cells	Thalidomide, Lenalidomide, Pomalidomide
Proteasome inhibitors	Proteasome inhibition stimulates multiple apoptotic pathways that are suppressed in MM. Lxazomib is an oral proteasome inhibitor.	Bortezomib, Carfilzomib, Ixazomib
Novel alkylators	Acts by combining an alkylator structure with a purine analog ring.	Bendamustine
Monoclonal antibodies	Anti CD38 monoclonal antibody Anti SLAMF7, a signalling lymphocytic activation molecule	Daratumumab Elotuzimab
Histone deacetylase (HDAC) inhibitors	Inhibition of histone deactetylator enzymes involved in the deacetylation of histone and non-histone cellular proteins making MM cells more sensitive to death receptor-mediated apoptosis and also inhibit IL-6	Panobinostat, Vorinostat
Selective Inhibitors of Nuclear Export (SINE)	Blocks exportin (XPO1) which shuttles tumor suppressor proteins from the nucleus to the cytoplasm, allowing them to accumulate in the nucleus and block oncoprotein mRNA translation	Selinexor

There are several combinations of drugs used in MM with varying degrees of clinical response (17,20–23). The current United States National Comprehensive Cancer Network (NCCN) guidelines recommend triplet therapy with a combination of bortezomib, lenalidomide and dexamethasone, or bortezomib, cyclophosphamide and dexamethasone as the standard of care for newly diagnosed MM patients who are transplant eligible. For those who are not transplant eligible, one can additionally use lenalidomide and low dose dexamethasone (24). The European Society for Medical Oncology (ESMO) also recommends use of triplet therapy as well for those aged less than 65 years and physically fit or less than 70 years and in good medical condition, high dose therapy with bortezomib and dexamethasone combine with either thalidomide or cyclophosphamide can be given prior to ASCT. Bortezomib, melphalan and prednisone or lenalidomide with low dose dexamethasone is recommended for elderly patients or non-transplant eligible patients (25).

Goals of treatment are to give optimal therapy which will give a deep response with few side effect profile that will be tolerable for individual patient taking into consideration any co-morbidities. The choice of therapy must also be accessible. The latter being a major determinant of choice of first line treatment.

Figure 1: Algorithm for treatment of multiple myeloma (Adopted from ESMO Clinical Practice Guidelines 201725)



CTD - cyclophosphamide, thalidomide, dexamethasone;
MP - melphalan, prednisone;
MPT - melphalan, prednisone, thalidomide;
PAD -bortezomib, doxorubicin, dexamethasone;
Rd - lenalidomide, low-dose dexamethasone;
RVD - lenalidomide, bortezomib, dexamethasone;
VCD - bortezomib, cyclophosphamide, dexamethasone;
VMP - bortezomib, melphalan, prednisone;
VRd,- lenalidomide, low-dose dexamethasone, bortezomib;
VTD - bortezomib, thalidomide, dexamethasone.

Treatment of refractory MM

Relapsed and refractory MM is more challenging to treat. Novel agents such as monoclonal antibodies, HDAC inhibitors and more recently Selective Inhibitors Of Nuclear Export (SINE) are recommended for refractory MM (23,26). For newly diagnosed MM patients, daratumumab, a monoclonal antibody, has been used in trials with the standard regimen of bortezomib, melphalan and prednisone in transplant-ineligible patients and led to lower rates of disease progression and death but with significant increase in grade 3 and 4 infections compared to placebo (27). Promising advances in MM treatment include Car-T therapy, originally developed for lymphomas, which involves using targeted T-cells to clear MM cells has shown some success in MM in select centres (28). A drug combination of monoclonal antibodies and

chemotherapy (ADC) agents is also in development phase (29). Bispecific T-cell engager antibodies (BiTes) that target surface antigens on MM cell and links them to CD3 on T-cells for clearance are also a promising intervention (30).

Discussion

The standard of care treatments of MM are expensive and remain inaccessible to most patients from low-and-middle income countries (4). Several Asian countries have adopted a regional resource-stratified standard of care for MM based on availability and affordability of novel drugs in their setting (31). Dexamethasone remains a cornerstone of therapy, with a combination of at least one novel drug, thalidomide or bortezomib (dual-therapy). Bortezomib is recommended for those with renal failure or increased risk of thrombosis. In the complete absence of novel drugs, they recommend dexamethasone combined with cyclophosphamide or vincristine and liposomal doxorubicin (31).

As at 2004, Othieno-Abinya *et al* (9), found that the standard treatment of MM at Kenyatta National Hospital, the main cancer treatment centre in Kenya, was melphalan-prednisone with/without thalidomide, which is similar to that of other African countries (5,26). Introduction of a novel agent, such as an IMID or PI, has been associated with better outcomes with one study reporting that bortezomib added to the standard melphalan and prednisone treatment had a higher partial and complete response rate, 71% and 35% respectively, compared to melphalan and prednisone alone at 30% and 4% for complete and partial response respectively (33). In 2016, the government has through the National Health Insurance Fund (NHIF) committed itself to covering the care of cancer patients including procurement of newer agents and facilitating access to transplant therapy abroad (34). Previously out-of-reach drugs such as bortezomib and lenalidomide became available in Kenya at an affordable price through the NHIF. There is an ongoing study on the treatment regimens for MM at Kenyatta National Hospital.

An important aspect in the management of MM patients is the need for supportive treatments for complications arising from the disease itself and occasionally from chemotherapeutic agents. This substantially adds to the resource consumption at health facility level adding to the economic cost of the disease. Patients with bone lesions on conventional imaging or serum hypercalcemia are generally started on intravenous bisphosphonates (35). Symptomatic vertebral compression fractures and long bone fractures may require surgical orthopaedic intervention. Pain that is refractory to medical and surgical interventions, impending pathological fractures as well as spinal cord compression are indications for low dose radiation therapy (10-30 Gy) (35). Persistent anaemia from the disease itself as well as following chemotherapy may require erythropoetic agents or/and blood transfusions. Vaccinations and prophylaxis against PCP, herpes and antifungals is required when patients are on high dose steroids and particularly so for herpes zoster in patients receiving bortezomib. For those on IMIDS, concurrent thrombo-prophylaxis for the entire duration of treatment is recommended. Overt renal failure may require dialysis or transplant and may therefore MM patients require adequate hydration, avoidance of nephrotoxic agents and monitoring while on bisphosphonates (35). The economic burden of MM therefore involves recognising the effect of the prevalence of complications of MM and the expected cost of the supportive management they require on the existing health system (36).

Conclusion

Multiple myeloma is a haematological disorder with varied systemic presentation and a more chronic progression with poor outcomes. However, with advances in treatment with biological agents and newer immunomodulatory drugs, there is increased progression and overall survival with relatively minimal adverse effects compared to previous treatments. Anticipation and provision of prompt supportive therapy such as renal replacement therapy, hydration and transfusion of blood and blood products would further improve survival of MM patients.

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Case report

Spinocerebellar Ataxia Type 2 (SCA-2): Case Series of Affected Individuals in a Large Family from Western Kenya

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Abstract

Spinocerebellar Ataxia Type 2 (SCA2) is an inherited Autosomal Dominant Cerebellar Ataxia (ADCA) characterized by progressive cerebellar ataxia, nystagmus, slow saccadic eye movements, and in some individuals, ophthalmoparesis or parkinsonism. Deep tendon reflexes are brisk early on and absent later in the course. Age of onset is typically in the fourth decade with 10-15 year disease duration.

We report a case series from an affected family who presented at Moi Teaching and Referral Hospital in Eldoret, Kenya. Genetic testing revealed a CAG repeat expansion (>33) at the ATXN2 (SCA2) gene locus with one normal and one fully expanded allele. To the best of our knowledge, this is the first case of genetically proven SCA-2 to be reported in the literature from Kenya. Healthcare workers need to be aware of its clinical presentation so as to have a high index of suspicion to aid early diagnosis.

Key words: Spinocerebellar ataxia type 2, Autosomal dominant, CAG repeats, Trinucleotide repeats, Western Kenya

Introduction

Spinocerebellar Ataxias (SCA) are clinically heterogeneous neurodegenerative disorders, characterized by progressive ataxia presenting alone or in combination with other neurological features. The genetic abnormalities are variable and include repeat expansions in coding and noncoding regions of genes, conventional mutations, or large gene rearrangements. This explains in part, clinical manifestation heterogeneity as well as differences in age of onset, disease severity, and progression (1).

Over 30 types of SCA's have been identified. The prevalence is estimated to be 1-4/100,000 (2). However, only 60-75% of patients have mutations in the known loci (2). Among SCAs caused by the repeat CAG-repeat expansions, includes SCA1, SCA2, SCA3, SCA6, SCA7 and SCA17, are the most common (1). Other repeat- associated ataxia disorders often have repeat expansions in the noncoding regions of the genes, such as SCA8, SCA10, SCA12. The rest of the relatively rare SCAs are often associated with the sequence alterations in the coding region (3). Different types of CAG-repeat SCAs have different rates of disease progression. For example, SCA1 progresses most quickly, followed by SCA3, and SCA2. SCA6 has the slowest rate of progression among the subtypes (4,5).

The proposed pathomechanism of the common CAG-repeat SCAs is that the polyglutamine, and the associated repeats exert toxic effects on the neurons or cause loss of the normal function of respective proteins (3). Intraneuronal inclusions can be seen in CAG-repeat SCAs (6). However, the pathomechanism of SCAs of non-CAG repeats in the noncoding regions is proposed to be primarily due to RNA toxic gain of function. The SCAs associated with sequence alterations are often due to disturbed protein function from the genetic mutations (7).

Each SCA has distinct but overlapping clinical features. In this case of SCA2, gene alterations include CAG repeats in ATXN2 and often patients have slow saccades, truncal titubation, hyporeflexia, and tremor. Although the clinical symptoms are helpful in pinpointing the correct genetic diagnosis, there is a strong ethnic predilection. SCA2 is very common in Cuba (8), and rare cases reported in Africa.

Although the treatment for SCAs remains only modestly effective, several novel therapies are currently being tested, including pharmacologic therapy, brain stimulation, and antisense oligonucleotides.

We present a case series from an affected family who presented at Moi Teaching and Referral Hospital in Eldoret, Kenya.

Ethical considerations: Genetic testing in cognitively impaired individuals poses a practical ethical dilemma. In our case, unaffected sibling acted as a surrogate representative of the patients, some of whom had

mild cognitive impairment. Pre and postest counselling were done to the patients and family. The patients were not subjected to any coercion and voluntarily underwent genetic testing and other routine clinical care tests. Informed consent was obtained from the surrogate representative and assent from the patients. Ethical approval was sought from the Institutional Review and Ethics Committee (IREC).

Genetic analysis: DNA was extracted from peripheral blood and the disease-associated repeat regions analysed by PCR and capillary electrophoresis. Fragment analysis and sizing was performed using Genemapper v.4.1 (Thermofisher scientific). The family tree and results of the genetic tests are shown in Figure 1 and Table 1 respectively.

Figure 1: SCA 2 genetic tree

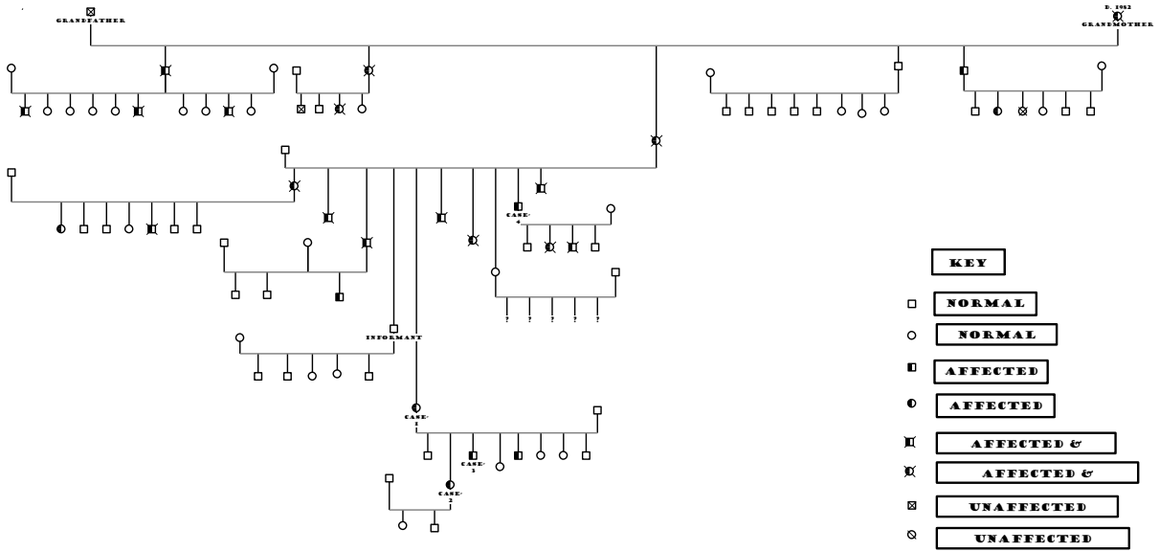

Table 1: Demographic, genetic and clinical data

Case no.	Age (years)	Gender	No. of CAG repeats/ Expansions	Disease duration (years)
1	50	Female	24/40	23
2	25	Female	21/45	4
3	18	Male	22/41	7
4	36	Male	19/42	8

Case reports

Case 1: A 50-year-old female who presented with complaints of slurring of speech and difficulty in walking. The symptoms began at the age of 27 years and were progressive with the speech gradually worsening. This was followed 8 years later with progressive difficulty in walking and limb tremors. Currently she is able to walk with support. There was no reported history of fevers, convulsions, cough, dysphagia, incontinence or weight loss. At presentation, her BP 129/83mmHg, pulse rate 104 beats/minute, temperature 36.7^{0}C, respiratory rate of 16 breaths/min and $Sp0_2$ 97% (at room air). On Central Nervous System (CNS) exam, she had a Glasgow Coma Scale (GCS) of 15/15 with impaired long term memory. On cranial nerves examination; she had slow saccadic eye movements with horizontal nystagmus. She had dysarthria with no tongue atrophy or fasciculation. On motor examination there was atrophy of the thenar and hypothenar muscles. The tone and power was normal while the deep tendon reflexes were absent in all the four limbs. There was reduced pin prick and fine touch sensation in a glove and stocking distribution and loss of vibration sense in both upper and lower limbs. She had an ataxic gait. She had past pointing on finger nose test as well as impaired heel sheen test. Dysdiadochokinesia was also present. The rest of her systemic examinations were essentially normal.

Her complete blood count, renal, liver function tests, creatine phosphokinase levels were normal. VDRL and HIV tests were negative. The ECG and ECHO were normal. MRI brain showed moderate cerebellar atrophy. Nerve conduction studies showed features of mild peripheral neuropathy. Genetic testing showed a CAG repeat expansion at the ATXN2 (SCA2) gene locus.

Case 2: A 25-year-old female patient, who is the second born daughter to case 1, presented with a history of progressive slurring of speech and unsteadiness in walking since four years ago. This was later followed by limb tremors and involuntary head jerky movements. There was no reported history of fevers, blurring of vision, or convulsions. At presentation, her BP 109/70mmHg, pulse rate 89 beats/minute, temperature 36.7^{0}C, respiratory rate of 17 breaths/min and $Sp0_2$ 98% (on room air).

On Central Nervous System (CNS) exam, she had a Glasgow Coma Scale (GCS) of 15/15 with poor long term memory and dysarthria. She had slow saccadic eye movement with vertical and horizontal nystagmus. On motor assessment, she had atrophy in the thenar and hypothenar muscles with reduced tone and a near normal power (4/5). Deep tendon reflexes were absent in all the four limbs. There was reduced pinprick and fine touch sensation in a glove and stocking distribution pattern. Vibration sense was reduced in both the upper and lower limbs. She had impaired finger nose test and dysdiadokokinesia was evident. She was unable to stand or walk due to excessive unsteadiness and was therefore wheelchair dependent. The rest of her systemic examinations were essentially normal.

Her blood tests (as in case 1) were all normal. The ECG and ECHO were normal. MRI brain revealed cerebellar atrophy. Nerve conduction studies showed features of peripheral neuropathy. Genetic testing showed a CAG repeat expansion at the ATXN2 gene locus.

Case 3: An 18 year old male patient, who is the third born son to case 1 presented with chief complaints of progressive unsteadiness during walking and slurring of speech. The symptoms began when he was 11 years of age. At presentation, his BP 143/81mmHg, pulse rate 112 beats/minute, temperature 36.7^0C, respiratory rate of 17 breaths/min and $Sp0_2$ 98% (at room air). On Central Nervous System (CNS) exam, he had a Glasgow Coma Scale (GCS) of 15/15. He had slow mentation and slow saccadic eye movement with vertical and horizontal nystagmus and dysarthria. His muscle bulk and power were normal in all limbs. He was areflexic in all four limbs. On the sensory examination, he had reduced pin prick and fine touch sensation in a glove and stocking distribution with reduced vibration sense in both upper and lower limbs. Joint position sense was normal. He had impaired finger nose test, heel sheen test and a positive Romberg's test. His gait was broad based and ataxic. The rest of his systemic examinations were essentially normal.

His blood tests (as for case 1) were normal. The ECG and ECHO were normal. MRI brain showed brain atrophy and the nerve conduction studies showed features of minimal sensory neuropathy. Genetic testing showed a CAG repeat expansion was detected at the ATXN2 gene locus.

Case 4: A 36-year-old male patient. A younger brother to case 1, presented with difficulties in walking, slurring of speech, poor co-ordination of movements and loss of sphincter control. He also had dysphagia and body tremors. The symptoms began when he was 28 years old. At presentation, his BP was 126/89 mmHg, pulse rate 101 beats/minute, temperature 36.8^0C, respiratory rate of 18 breaths/min and $Sp0_2$ 99% (on room air). On Central Nervous System (CNS) exam, he had a Glasgow Coma Scale (GCS) of 15/15. On cognitive function, the domains affected were orientation, memory and praxis. He had dysarthria with slow saccadic eye movement but no nystagmus. On motor examination, he had muscle atrophy in both upper and lower limbs with areflexia in all four limbs. The rest of his systemic examinations were essentially normal.

His blood tests (as in case 1) were normal. The ECG and ECHO were normal. MRI showed brain atrophy with severe cerebellar atrophy. Nerve conduction studies showed features of mild peripheral neuropathy. Genetic testing showed a CAG repeat expansion at the ATXN2 (SCA2) gene locus.

Discussion

In early 2019, a Kenyan media house reported that a 'mysterious disease' had claimed the lives of eleven family members in Londiani, Kericho County. A family spokesman appealed to medical experts to help them unravel the puzzle of the suspected fatal hereditary disease (9). Following his appeal, affected family members were brought to the Moi Teaching & Referral Hospital (MTRH) for investigations and management.

The evaluation of the affected family members revealed the 'mysterious' condition to be Spinocerebellar Ataxia type 2 (SCA-2). The affected persons had progressive cerebellar ataxia, nystagmus, slow saccadic eye movements, features of peripheral neuropathy and cognitive dysfunction but no ophthalmoparesis or parkinsonism. MRI brain revealed cerebellar atrophy in all the cases with NCS indicating features of peripheral neuropathy. Molecular genetic testing to detect an abnormal CAG trinucleotide repeat revealed an expansion in ATXN2 gene. Affected individuals had alleles with 33 or more CAG trinucleotide repeats.

To the best of our knowledge, this is the first case of genetically proven SCA-2 to be reported in the literature from Kenya. Previous case reports have been reported from other African countries (10-15).

Our case series spans three generations with the original presentation in the family tree being traced to their great grandmother. Many early deaths have occurred in the family largely attributable to the disease. Genetic anticipation was evident in the family with subsequent generations being affected early and presenting with more severe symptoms.

Symptomatic management of those affected included physiotherapy, use of assistive walking devices for those who were not yet wheel chair

dependent, management of decubitus sores, treatment of aspiration pneumonitis, DVT prophylaxis, bladder and bowel care, assisted feeding and vitamin supplementations. Genetic counselling was provided to family members given that the offspring of an affected individual has a 50% chance of inheriting the causative CAG trinucleotide repeat expansion.

Conclusion

This is the first case of genetically proven Spinocerebellar Ataxia type 2 (SCA-2) to be reported in Kenya. Healthcare workers need to be aware of its clinical presentation so as to have a high index of suspicion to aid early diagnosis. In this case, the diagnosis had been delayed despite the affected family members seeking care in some health facilities. The role of the media in highlighting such conditions to create awareness and reduce stigma cannot be overemphasized.

Recommendation

Kenya wide epidemiological studies are needed to establish the true prevalence of spinocerebellar ataxias. Establishment of support groups for the affected families is necessary to deal with issues of stigma, disability and healthcare costs.

Acknowledgements

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Case report

Cardiac Arrest Due to Acute Myocardial Infarction Immediately After Induction of General Anaesthesia: Case Report

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Abstract

Peri-operative myocardial infarction is a common condition that contributes to significant morbidity and mortality in non-cardiac surgery patients. Unlike spontaneous acute myocardial infarction, perioperative myocardial infarction presents a diagnostic challenge because patients have no chest pain due to anaesthesia or sedation, electrocardiogram changes are subtle and biomarkers like CK-MB may be non-specific due to co-existing skeletal muscle damage from surgery or a consequence of other non-myocardial ischemia related elevation in troponin as happens in severe sepsis and pulmonary embolism. Management of perioperative myocardial infarction also poses a big challenge due to significant risk of bleeding with antiplatelet, anticoagulant and fibrinolysis, the cornerstone drugs for management of acute myocardial infarction.

We report the case of a 67-year-old hypertensive male who developed acute perioperative myocardial infarction shortly after induction of anaesthesia for an elective laminectomy post traumatic vertebral compression.

Key words: Peri-operative, Myocardial infarction, Electrocardiogram,troponins, Anaesthesia, Cardiac arrest

Introduction

Peri-operative myocardial infarction is a common condition that contributes to significant morbidity and mortality in a non-cardiac surgery patients (1,2). Unlike spontaneous acute myocardial infarction, perioperative myocardial infarction presents a diagnostic challenge because patients have no chest pain due to anaesthesia or sedation, electrocardiogram changes are subtle and biomarkers like CK-MB may be non-specific due to co-existing skeletal muscle damage from surgery or a consequence of other non-myocardial ischemia related elevation in troponin as happens in severe sepsis and pulmonary embolism (3,4).

Case report

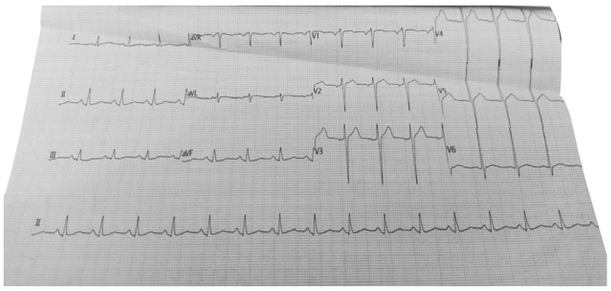
We present the case report of a 67-year-old male recently diagnosed hypertensive (six months prior to admission) on amlodipine 10mg admitted for elective neck surgery; fusion of C5-C7 following a Road traffic accident that resulted in C5-C7 vertebra body compression fractures with spinal cord compression. Surgery was scheduled to be performed without cardiac work up as the patient was presumed to be have a low cardiovascular disease risk. His physical status was assessed as American Society of Anesthesiologists class I.

Preoperative laboratory work up was unremarkable: haemoglobin and haematocrit were 13.3 g/dL and 37.0%, respectively. Other preoperative laboratory findings including renal function were within normal reference range for our laboratory. No premedication was administered prior to induction of anaesthesia. In theatre, the patient was connected to a monitor with pulse oximeter, end tidal CO_2, continuous blood pressure and ECG monitoring. Before induction his baseline blood pressure was 165/78mmHg, heart rate 98 beats/min, oxygen saturation at 98% and body temperature was 36.4^0C. Pre-oxygenation was done with 100% oxygen at 8l/min. Anaesthesia was induced with intravenous propofol 150mg and suxamethonium 100mg. Patient was successfully intubated without difficulty using an endotracheal tube, RAE cuffed 7.5mm. Anaesthesia was maintained with isoflurane 0.6% and oxygen. atracurium 50mg was administered as the long acting muscle relaxant. Two minutes into the maintenance of anaesthesia, patient heart rate dropped to 34 and intravenous atropine 1mg was administered. Shortly after, the patient went into asystole. Cardiopulmonary resuscitation (CPR) was commenced immediately with continuous chest compression and breaths being given every 5 seconds. 1mg of intravenous epinephrine was administered after 2 minutes. After the first cycle of CPR the patient had a Return of Spontaneous circulation (ROSC). Surgery was cancelled and the patient was reversed

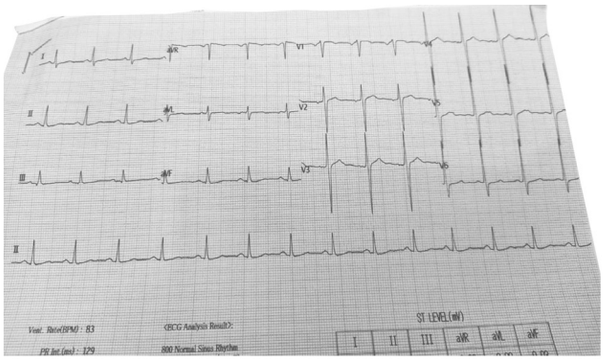
after 45 minutes after atracurium wore off using intravenous neostigmine 2.5mg and atropine 1.2mg.

He was transferred to High Dependency Unit (HDU) through Post Anaesthesia Care Unit. Upon arrival in HDU, blood pressure was 136/80 mmHg, heart rate of 79beats/min, random blood sugar 5.8mmol/l, body temperature 36.1^{0}C, and SpO_2 was 98% on room air. A 12 lead ECG was significant for ST elevation in leads V3, V4, and V5. Laboratory tests revealed marginally elevated troponin I 68.2ng/ml (17-50ng/ml). Two dimensional transthoracic echocardiogram revealed features of ischemic heart disease involving apical septum, apex and mid apical lateral walls with a normal Ejection Fraction (EF) of 55% without any evidence of post myocardial infarction complications.

Figure 1: ECG on day 1 showing ST elevation V1,V2,V3 which normalized by day 7



ECG on first day



ECG seven days later

The patient was put on a daily oral acetylsalicylic acid and clopidogrel at 75mg after a loading dose of 300mg each. He was also started on subcutaneous enoxaparin 60mg twice a day and oral atorvastatin 80mg. He continued with his oral amlodipine 10mg for blood pressure control.

He was discharged home after a seven day stay in hospital to have a coronary angiogram and cardiology review. He was also booked for follow up in our medical outpatient clinic and the neurosurgical outpatient clinic. Conservative management for the spinal injury pending further reconstructive surgery after full recovery was also advised.

Discussion

The Third Global MI Task Force defines myocardial infarction as myocardial necrosis in the setting of myocardial ischemia characterized by a rise in biomarkers e.g. troponin along with any of the following (1);

(i) Cardiac symptoms of ischemia
(ii) New or presumed new significant ST-segment and T wave changes or new left bundle branch block
(iii) The development of pathological Q waves in the electrocardiogram (ECG)
(iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;
(v) The identification of an intracoronary thrombus by angiography or autopsy

Peri-operative myocardial infarction occurs in a surgical patient during induction of anaesthesia, intraoperatively or in the immediate post-operative period. Perioperative Myocardial Injury (PMI) is an important but commonly undetected complication after non cardiac surgery that is strongly associated with a high mortality and morbidity including re-hospitalisation, heart failure amongst others (2-4). In contrast with spontaneous Myocardial Infarction (MI), PMI is clinically silent and doesn't exhibit typical symptoms of myocardial ischemia such as chest pain, angina pectoris, or dyspnea, and is therefore missed in routine clinical practice (2-4).

The incidence of PMI varies widely because of heterogeneity in study designs, study populations, case definition employed as well as types of surgery. Various large-scale studies have revealed a diverse incidence of ranging from 0.3 to 16% (2,4). In POISE (Peri-Operative Ischemic Evaluation) in a multicenter prospective study of 8351 patients in 192 centers across 23 countries, Devereaux *et al* (2) found an incidence of 5%. Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION), another large study by Devereaux *et al* (4) found an incidence of 16%. In a retrospective study, Smilowitz *et al* (5) reported a 0.9% acute myocardial infarction occurrence in patients aged 45 years or older undergoing major non-cardiac surgery in the United States from 2005 to 2013.

Mortality from perioperative myocardial infarction is high 10-16% (2,4,6). Puelacher *et al* (6) in a prospective diagnostic study that enrolled 2546 non cardiac surgery patients found a crude 30-day mortality of 8.9% (95% confidence interval [CI], 5.7–12.0) in patients with PMI versus 1.5% (95% CI, 0.9–2.0) in patients without PMI. This trend was replicated at one year where 64 of 285 (22.5%; 95% CI, 17.9–27.8) patients with PMI versus 160 of 1733 (9.3%; 95%

CI, 8.0–10.8; *P*<0.001) patients without PMI had died. In POISE trial the attributable 30-day mortality rate was five times in the PMI group compared to the non-PMI group (2).

Myocardial Injury after Non Cardiac Surgery (MINS) is defined as myocardial injury caused by ischemia that occurs during or within 30 days of surgery. Criteria for diagnosis for MINS was defined in the recent universal MI definition as a prognostically relevant postoperative troponin level elevation during or within a period of 30 days after non-cardiac surgery with:

(i) An underlying ischemic origin of troponin elevation (absence of non-ischemic aetiology such as rapid atrial fibrillation, pulmonary embolism, sepsis, etc.)
(ii) Absence of other clinical or ECG criteria of PMI.
(iii) The extent of troponin elevation has been generally defined as greater than 99th percentile of the UNL of the particular assay

MINS is independently associated with mortality (4, 6). However patients with MINS have a lower incidence of adverse cardiac events compared to those with PMI but higher than patients without elevated cardiac biomarkers (6). Without perioperative troponin monitoring, 93.1% of MINS, 68.0% and 82% of PMI might go unrecognized because these patients do not experience ischemic symptoms (4,6,7).

Unlike spontaneous acute myocardial infarction, perioperative myocardial infarction presents a diagnostic challenge because most patients have no chest pain due to effects of anaesthesia and sedation, subtle electrocardiogram changes and biomarkers like CK-MB may be non-specific due to co-existing skeletal muscle damage (4,6,7). A high index of suspicion as well as continuous monitoring of these patients is necessary for the diagnosis.

Risk factors for PMI include traditional risk factors for spontaneous myocardial infarction as well as those related to anaesthesia and surgery. These risk factors include : poor cardiac status, diabetes mellitus, chronic kidney disease, cerebrovascular accident, hypertension, smoking, dyslipidemia, major surgery, intra-operative blood transfusion, peri-operative hypotension and hypertension, recent percutaneous coronary intervention and inappropriate peri-operative analgesia (9).

Majority of PMI occur within 48 hours of surgery. In a retrospective study in China, Zhou *et al* (10) found out of 45 PMI patients only a single case occurred during the induction of anaesthesia, 27 (60%) cases within 48hour of surgery and 18 (40%) cases after 48hours. Moreover, the onset of PMI was detected later in the mortality group than in the survival group (10). Landesberg *et al* (11) found 20% of PMIs develop in the operating room while most PMIs i.e. 80% manifest 48–72 hours postoperatively. Despite the early onset, diagnosis of PMI is always delayed and majority is made on 3-5th post-operative days (12). Clinical presentation of PMI differs markedly from that of spontaneous AMI. Chest pain the principal symptom in spontaneous acute myocardial infarction is uncommon in PMI. In the Vascular Events in Non-cardiac Surgery Patients Cohort Evaluation (VISION) trial 68% of patients didn't experience ischemic symptoms (4).

In another large study a majority of patients with PMI, 325 of 397 (82%), did not show any ischemic symptoms, and chest pain was only present in 24 of 397 (6%). ECG findings suggestive of myocardial ischemia, especially ST-segment depression or T-wave inversion, were observed in 60 of 244 (24%) of ECGs performed. Together with an additional seven patients showing evidence of loss of viable myocardium on imaging, overall only 117 of 397 (29%) of patients fulfilled any of the additional criteria required for spontaneous AM beyond the increase in highly sensitive troponin. These prospective observations corroborate that these acute events would in the vast majority have been missed in the absence of systematic screening (6).

Haemodynamic instability is however common in PMI with a prevalence of more than 80% in the POISE trial (2). The anaesthesiologist should always remain alert for early detection of intra-operative complication by continuously monitoring the heart rate, blood pressure and electrocardiogram.

Two different mechanisms lead to PMI. Type 1 PMI is caused by sudden rupture of a vulnerable coronary plaque and subsequent platelet aggregation or by severe coronary vasospasm. These cause either occlusive [ST-segment elevation, STEMI) or non-occlusive (non-ST-segment elevation (NSTEMI)] thrombus, and myocardial infarction. Plaque disruption is demonstrated in autopsy studies in approximately 50% of patients who succumb to PMI (14). Type 2 PMI usually occurs due to sustained imbalance between myocardial oxygen supply and demand in coexisting significant, obstructive, although not occlusive coronary heart disease. Therefore, majority of patients with PMI type 2 demonstrate ST-segment depression (NSTEMI).

Multiple scoring systems are available that predict the risk of major adverse effects perioperatively based on past medical and surgical history. In major elective non cardiac surgery, Lee and colleagues in 1999 outlined revised Cardiac Risk Index to predict major cardiac complications as it is simple, validated and widely used. It includes ischemic heart disease, high risk surgery, stroke or transient ischemic attack, prior heart failure, preoperative insulin therapy and creatinine level >2mg/dl (15).

European Society of Cardiology joint guidelines recommend ECG to be recorded at baseline, immediately after surgery and on the first 2 days following surgery and biomarkers to be obtained for all high-risk patients.

In accordance with the 2014 European Society of Cardiology/European Society of Anaesthesiology (ESA/ESC) guidelines, the assessment of cardiac troponin both before and 48–72 hours following major surgical procedures, may be considered in high-risk patients (class IIb, level B). Patients with preoperatively higher troponin levels may undergo a baseline transthoracic echocardiogram (for assessing ventricular function and regional wall motion), a cardiology consultation, and deferral of surgery till the troponin levels settle (15).

The major difference between perioperative patients and non-surgical patients is the risk of life-threatening bleeding and thus thrombolysis is almost always contraindicated in PMI. Aggressive use of antiplatelet agents and anticoagulants may also increase bleeding. Management of PMI is a complex and very dynamic area with paucity of data and more research is needed.

Conclusions

Rapid diagnosis and treatment of suspected acute MI in perioperative patients is crucial to reduce the mortality and morbidity. However this presents a diagnostic challenge as most PMI are clinically silent. A high degree of suspicion is thus necessary. There is paucity of data on PMI in Africa and specifically Kenya and research is needed in this area. For patients scheduled for non-cardiac surgery who are 50 years and above with known cardiovascular disease risk factors, pre-operative cardiac assessment is recommended.

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