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Kidney disease in hospitalised HIV positive children in Ibadan, South West Nigeria

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Abstract

Background: There is a paucity of data on the clinicopathologic pattern of kidney disease in Human Immunodeficiency Virus (HIV) seropositive children from sub-Saharan Africa and non from South West Nigeria.

Objective: To determine the clinical pattern and outcome of kidney disease among HIV positive children hospitalised at a tertiary hospital South West Nigeria

Methodology: A retrospective study of all HIV positive children who were hospitalised and managed for kidney diseases over a period of 78 months at the University College Hospital Ibadan, South West Nigeria. Patients were followed up over the duration of hospital admission.

Results: Ten children (six males and four females) aged 4 -15(10.4±3.2) years were identified. Four presented in acute kidney injury, (AKI) three with nephrotic syndrome (NS) and two in chronic kidney failure (CKF). One patient had left renal artery stenosis. Renal biopsy performed in three children showed focal segmental glomerulosclerosis in two patients and membranous nephropathy in the third. Management included antiretroviral therapy, Angiotensin Converting Enzyme Inhibitors and acute haemodialysis. Mortality was 40%.

Conclusion: AKI, NS and CKF were the predominant clinical patterns of kidney disease in hospitalised HIV positive children and the mortality is high.

Keywords: *HIV, Children, Acute Kidney Injury, Chronic kidney Failure, Nephrotic Syndrome, Nigeria*

Résumé

Contexte: Il ya un manque de données sur le modèle anatomo-clinique de la maladie rénale chez les enfants séropositifs en Afrique sub-saharienne ce qui n'est pas le cas au Sud-ouest du Nigeria.

Objectif: Déterminer le profil clinique et l'issue de la maladie rénale chez les enfants séropositifs hospitalisés dans les centres hospitaliers publics au Sud-ouest du Nigeria.

Méthodologie: Une étude rétrospective sur tous les enfants séropositifs qui ont été hospitalisés et qui suivaient des traitements relatifs aux maladies rénales pendant une période de 78 mois au Centre hospitalier universitaire d'Ibadan au Sud-ouest du Nigeria a été faite. Les patients ont été suivis pendant toute la durée d'hospitalisation.

Résultats: dix enfants (six garçons et quatre filles) dont l'âge varie entre 4 et 15 ans (10,4 ± 3,2) ont été identifiés. Parmi eux, il y avait quatre cas de lésions rénales aiguës, (LRA) trois cas de syndrome néphrotique (SN) et deux cas d'insuffisances rénales chroniques (IRC). Un patient a été guéri de la sténose artérielle rénale. La biopsie rénale effectuée sur trois enfants a montré une glomérulosclérose segmentaire et focale chèz deux patients et une néphropathie membraneuse chez le troisième. Le traitement incluait la thérapie antirétrovirale, les inhibiteurs de l'ECA et l'hémodialyse aiguë. La mortalité était de 40%.

Conclusion: Les LRA, les SN et les IRC étaient les principaux modes cliniques de la maladie rénale chez les enfants séropositifs hospitalisés et la mortalité était élevée.

Introduction

Kidney disease is an important cause of morbidity and mortality in HIV seropositive patients. The pattern of clinical presentation is wide and includes proteinuria, fluid and electrolyte abnormalities, tubular disorders, nephrotic syndrome (NS), acute kidney injury (AKI), chronic kidney failure (CKF) and end stage kidney disease (ESKD) [1-3]. A clinically distinct entity is HIV-1 associated nephropathy (HIVAN), which is the most common cause of chronic kidney disease in HIV positive patients, with the majority of cases occurring in blacks [4-8].

HIVAN may be suspected on the basis of clinical criteria, but definitive diagnosis requires renal biopsy. Its pathogenesis involves a complicated

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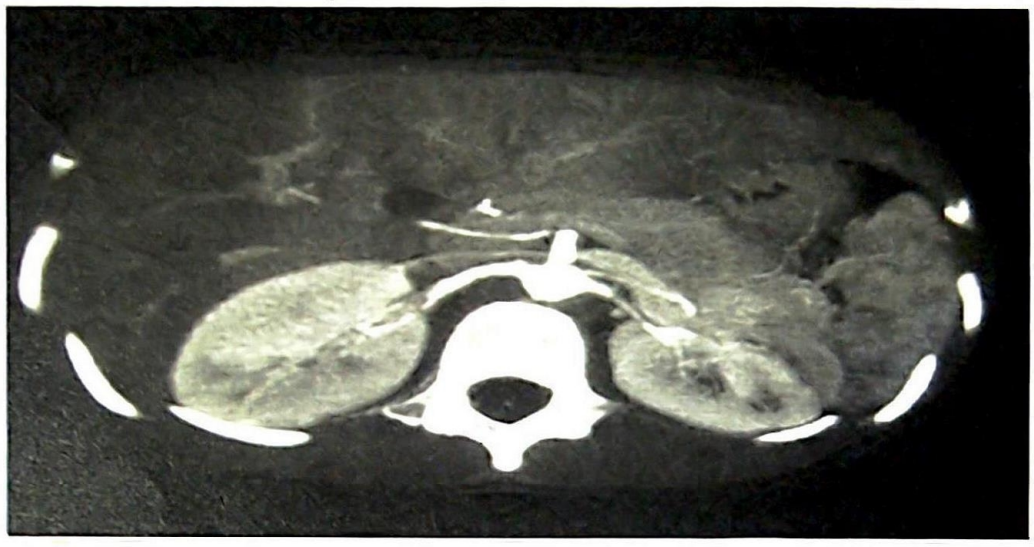

Fig 1: Contrast enhanced CT scan showing left renal artery stenosis (arrow) and compensatory right renal enlargement in an 11 year old HIV seropositive girl with hypertension.

Table 1: Demography, clinical presentation and co-morbidities in admitted HIV seropositive children with kidney disease

Patient No.	Age(Years)	Gender	Clinical Presentation	Co-morbidities
1	4	M	NS	Septicaemia
2	8	M	AKI	Septicaemia
3	10	M	NS, HTN	
4	10	M	NS	Kaposi sarcoma, urethritis,Acute osteomyelitis left femur, anterior urethral strictures
5	13	F	CKF/ESRD, HTN	
6	11	F	AKI, HTN	AIHA, septicaemia
7	15	F	AKI, HTN	Septicaemia vaginal discharge ,Genital ulcers, mouth ulcers
8	11	F	Lt RAS, HTN	
9	14	M	CRF, ESRD, HTN	
10	8	M	AKI, HTN	Meningitis,Pneumonia,Septicaemia

AIHA: Autoimmune Hemolytic Anaemia; AKI: Acute kidney injury; CKF: Chronic kidney failure; ESRD; End stage renal disease; HTN: Hypertension; Lt RAS: Left renal artery stenosis; NS: Nephrotic Syndrome

vertical in all patients. In HIV seropositive children who presented with kidney disease, the diagnosis of HIV infection was made 6 -22 (mean 15.0 ± 6.6) days after the onset of features of kidney disease.

Clinical presentation and co-morbidities

Oedema was present in 6 patients (60.0%). Table 1 shows the distribution of the clinical presentation and co-morbidities in the patients. Seven (70%) patients including one with renal artery stenosis (see Fig 1) had hypertension. Six (60%) patients were in renal failure, four (40%) had AKI, while two (20%) were in CKF. Three patients had NS.

Acute kidney injury was secondary to acute tubular necrosis in our patients and causes were septicaemia in three patients; and intravascular haemolysis in the fourth. The co-morbidities in one of the patients with NS were Kaposi sarcoma, acute osteomyelitis of the right femur and urethritis with urethral discharge. This patient subsequently developed anterior urethral strictures.

Laboratory investigations

Table 2 demonstrates the results of laboratory investigations performed in the children. Urine dipstick examination showed varying degrees of proteinuria in 9 patients (90%) with 4 (40.0%) having levels of ≥ 300mg/dL. Serum urea and creatinine levels among the 6 patients in renal failure ranged from 135-405 (247 + 122) mg/dL and 1.9-10.0 (5.9 ± 3.7) mg/dl respectively. The CD4 count, available for 8 patients, all of whom were aged 8 years and above, was 8 - 479 (168 ± 138) cells/ml, (median 136 cells/ml), while the RNA viral load measured in 4 patients (patients 3, 4, 5 & 8) ranged from <200-779803.0 copies/ml, (median, 9821 viral copies/ml). Abdominal ultrasound scan showed enlarged kidneys in four patients (40%) and normal kidney sizes in the others. Sonography of the kidneys also demonstrated increased parenchymal echogenicity in all the children. The five patients whose HBsAg screening records were available had negative results. Renal biopsy performed in three patients showed collapsing FSGS in patient 4, membranous nephropathy in patient 5, and collapsing FSGS with microcystic tubular dilatation in patient 7 (Fig 2).

Treatment and outcome

Seven patients received ART. Three started ART before onset of kidney disease with the duration of ART varying from 18 - 485 days before the diagnosis of kidney disease. Two of these patients showed immunologic failure with CD4 counts of 349 and 29 / ml respectively.

First line ART consisted of oral Zidovudine, with oral Lamivudine, and oral Nevirapine or Efavirenz, while second line drugs for patients who had clinical or immunologic failure were oral lamivudine, didanosine and lopinavir/retonovir. Of the patients who received ART, one died while three patients who did not receive ART died.

Four patients received the Angiotensin Converting Enzyme Inhibitor, oral Lisinopril, but mortality was recorded in one of the four patients. The mortality was in a patient who was in ESKD, and died from complications of renal failure. Steroids were not utilized in the treatment of any patient. Haemodialysis was performed in three patients, one in AKI, and two in CKF and ESKD. One of the patients in CKF and ESKD who had very low residual kidney function and required chronic dialysis died from fluid overload and pulmonary oedema. The two other patients survived till discharge from the hospital.

Blood pressure in the patient with left renal artery stenosis was controlled with oral nifedipine, methyldopa and atenolol. Anterior urethral stricture (in patient 4) was managed surgically. The duration of hospital stay for the children ranged from 2-147 (median 37.5) days. The patient who spent a total of 147 days on admission was admitted on three different occasions for 79, 35 and 33 days respectively.

Overall mortality was 40.0%. All the AKI survivors had recovered renal function by the time of discharge from the hospital while one of the patients with NS (patient 4) achieved remission by the time of discharge.

Table 3: Treatment and outcome in HIV positive children with kidney disease

Patient No.	ART	ACEIs	RRT	Outcome
1	-	-	-	Died
2	-	-	-	Died
3	AZT, 3TC, EFV	-	-	Alive
4	d4T, 3TC, NVP; 3TC, ddI, LPV/RTV	Lisinopril	-	Alive
5	AZT, 3TC, EFV;3TC,ddI, LPV/RTV	Lisinopril	HD	died
6	AZT, d4T, NVP	-	HD	Alive,
7	3TC, NVP, d4T	Lisinopril	-	Alive
8	3TC, AZT, NVP	-	-	Alive
9	d4T, 3TC, NVP	Lisinopril	HD	Alive
10	-	-	-	Died

3TC: Lamivudine; ACEIs: Angiotensin Converting Enzyme Inhibitors; AZT: Zidovudine; d4T: Stavudine; ddI: Didanosine; EFV: Efavirenz; HAART: Highly Active Antiretroviral Therapy; HD: Haemodialysis; LPV/RTV Lopinavir/Ritonavir; NVP: Nevirapine; RRT: Renal Replacement Therapy.

Discussion

There is limited published data on the pattern of kidney disease on HIV seropositive children in many parts of sub-Saharan Africa, the sub region most affected by the disease. There are no reports on the clinical spectrum of kidney disease among HIV positive children in South West Nigeria, our study documents the pattern of kidney disease among HIV positive children in South West Nigeria.

The findings that 90% of the patients were aged 8 years and above and were infected through the vertical route indicate that kidney disease was a late manifestation of HIV infection among our patients. Many studies from developed countries also indicate that kidney disease was a late feature of HIV infection [11,28-30]. Similarly, the finding that blood transfusion was not a route of HIV infection in any of the patients agrees with reports from developed countries where blood transfusion accounted for a negligible rate of HIV transmission [11,31,32]. It however contrasts with the observation from Port Harcourt in Nigeria which showed a high rate (40%) of blood transfusion acquired HIV infection among patients with HIVAN. Vertical transmission was recorded in only 30% of patients in that study [33]. The differences in the modes of transmission may be as a result of differences in the blood transfusion practices prevailing at the times the studies were undertaken.Reduction of mother to child transmission of HIV infection will go a long way in reducing paediatric HIV infection and hence prevent related kidney disease.

The finding of oedema and hypertension in many of the HIV seropositive children with kidney disease in our series is similar to the experience in Port Harcourt, South - South Nigeria [33]. Hypertension and oedema are however not usual features of HIVAN. Persistent proteinuria, in the absence of severe hypertension and oedema remains an early feature of HIVAN [11,19,34,35]. Microalbuminuria has also been identified as a predictor of HIVAN and proteinuria [14,36]. The high rates of hypertension and oedema in our study may have been due to the late presentation in our patients, many of whom were in AKI and CKF, coupled with inadequate access to renal replacement therapy. In addition, hypertension was secondary to left renal artery stenosis in one of our patients.

The kidneys exhibited increased echogenicity on abdominal ultrasound in 80% of the patients, and 40% of our patients had enlarged kidneys. Bilateral echogenic kidneys that are often enlarged are the usual finding in HIVAN, but some studies have indicated the presence of small or normal sized echogenic kidneys [10,28,33,37]. The echogenicity and enlargement of the kidney are presumably due to prominent interstitial expansion by cellular infiltration, and markedly dilated tubules containing echogenic, proteinaceous casts. On the other hand, normal or small sized kidneys may occur as a consequence of long standing kidney disease or previous episodes of recurrent acute pyelonephritis leading to CKF [3,33]. However a typical renal ultrasound appearance has not been described in most reports of AKI in HIV seropositive patients, possibly because the aetiology of AKI in HIV seropositive individuals is heterogeneous [38].

In the studies, conducted before ART became widely available in developed countries, HIVAN was associated with evidence of severe immunosuppression such as low CD4 counts, or development of opportunistic infections within 6 months of the diagnosis of HIVAN [30]. AKI in HIV seropositive patients has also been associated with more severe immunosuppression evidenced by low

Table 2: Laboratory profile in HIV seropositive children with kidney disease

Patient no	PCV	Serum urea	Serum Cr	Serum Alb	CD4 count (%)	HIV Viral load (copies/ml)	Dipstick Urinalysis	kidney size (USS)	Renal biopsy
1	10	29	0.7	1.8	-	-	NRP, H	Enlarged	-
2	12	322	6.0	-	-	-	P, H	N	-
3	28	59	0.7	1.4	479 (20.1)	121679	NRP, H	Enlarged	-
4	30	25	0.2	2.0	29(5)	779803	NRP	N	FSGS
5	22	339	10	3.5	349	76,163	P, H	N	MN
6	19	405	6.5	3.0	39 (6.93)	-	P, H	Enlarged	-
7	24	148	4.0	-	10 (3.7)	-.	P	N	-
8	34	19	0.8	4.2	380	<200	H	N	-
9	20	217	4.2	3.8	8	-	NRP,H	N	FSGS
10	22	137	1.9	-	124	-	P	Enlarged	-

Alb: Albumin; Cr: Creatinine; FSGS: Focal segmental glomerulosclerosis; H: Haematuria; MN: Membranous nephropathy; N: Normal; NRP: Nephrotic range proteinuria ; PCV: Packed cell volume; P: Proteinuria; USS: Ultrasound;

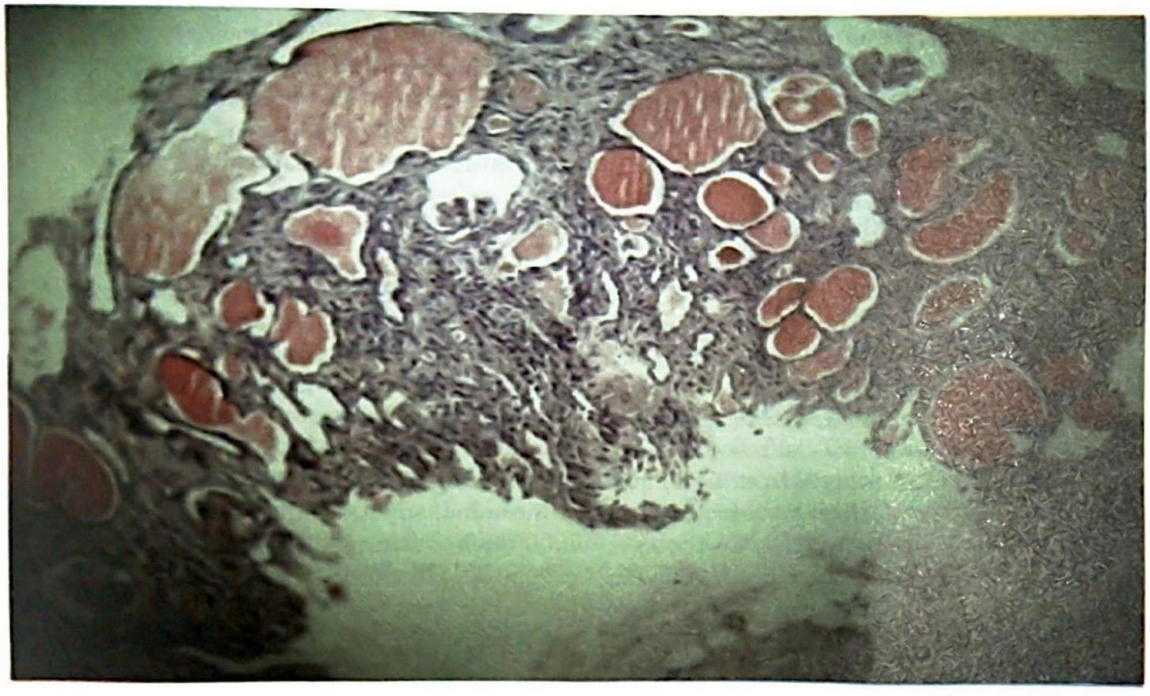

Fig 2: Photomicrograph of renal biopsy showing collapsing FSGS and microcystic tubular dilatation in patient 7 (H& E x160)

reduced immunity, increased likelihood of death from opportunistic infection, severe bacterial infections, AIDS defining illness and progression to end stage kidney disease [3,10,11,15,16,29,32,37]. The children with HIVAN in that era frequently died from opportunistic infections before developing ESKD, or shortly after commencing dialysis [10,15,32]. Since ART became widely available, however, a greatly increased number of children with HIVAN surviving and requiring chronic dialysis or kidney transplantation in the United States of America has been documented [10,19-21,29]. AKI in HIV adult seropositive patients has also been associated with poor prognosis with a mortality of 43-60% in the United States of America [29,42,63]. In Nigeria as in many parts of sub-Saharan Africa late diagnosis of HIV infection and HIV related kidney disease, the late commencement of ART, coupled with the absence of facilities for paediatric renal replacement therapy in many centres imply that co-morbidities such as septicaemia and complications of renal failure will be the main causes of death in HIV seropositive children with kidney disease.

Our study is limited by the small number of renal biopsies and short period of follow up. It also does not assess for sub clinical kidney dysfunction in other HIV positive children seen during the period of study, which may have contributed to the morbidity or mortality in these other children. It however highlights the morbidity, and high mortality associated with kidney disease and HIV infection in our country, and sub region. Furthermore with improvement in management of opportunistic infections in HIV seropositive children in the sub region, kidney disease may occur more frequently in the surviving cohort.

In conclusion, the spectrum of kidney disease in HIV seropositive patients is heterogeneous with AKI; NS and CKF as the predominant clinical presentation. Kidney disease in HIV seropositive children is associated with very high in-hospital mortality. Early detection of HIV infection in children, as well as kidney disease in those who are found to be seropositive, prompt use of ART and ACEIs as indicated may improve the outcomes in affected children. Facilities for paediatric renal replacement therapy should be provided in the country and prevention of mother to child transmission of HIV remains the ultimate goal.

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CD4 counts, and high viral load [39-41]. Consequently, the low CD4 count in our patients is in keeping with previous studies and supports the observation that kidney disease is a late finding in HIV infection.

Studies in adults indicate that HIV infected patients are at increased risk of acute kidney injury compared with individuals who do not have the virus [38,42,43]. AKI occurred with an incidence rate of 5.9 per 100 patient years in a cohort of 750 ambulatory HIV infected adult patients. Among hospitalised patients about 18% of HIV seropositive patents developed AKI with nearly a 2-3 fold higher risk of AKI compared with HIV uninfected patients [39,40,44,45]. AKI including mild elevations in serum creatinine has been associated with increased long term risk of ESKD, mortality or cardiovascular disease in HIV seropositive patients [45]. In Port Harcourt, South South Nigeria, AKI was the clinical manifestation of kidney disease in 50% of HIV seropositive patients [33], which is similar to the observation in this study.

The causes of AKI in HIV seropositive patients are usually not directly related to HIV infection as also shown in this study. All the cases of AKI in our study were secondary to acute tubular necrosis, which has also been observed to be a common cause of AKI in adult HIV seropositive patients, accounting for about 20% of cases [39,46]. Although prerenal azotaemia is noted to be the commonest cause of AKI in adult HIV infected patients [41], it was not a common finding in our series probably because patients with prerenal azotaemia were not routinely referred to the nephrologist. Furthermore none of our patients had AKI secondary to thrombotic microangiopathy, as observed in South Africa [46]. This may be related to the observation that HUS is not a common cause of AKI in Nigeria [38,47,48].

Five patients (50%) presented with NS or CKF. HIVAN initially manifests with proteinuria which may range from minimal to nephrotic range with oedema; and then progresses slowly or rapidly to end stage kidney disease [10,15,37]. In black HIV seropositive patients with glomerulopathy, HIVAN is the most frequently identified lesion [10,11,15,16,37]. Other reported histological findings include mesangial hyperplasia, minimal change and focal necrotizing glomerulonephritis, lupus like glomerulonephritis, membranoproliferative glomerulonephritis and membranous nephropathy [1,14-16,37,49]. Renal biopsies performed in three of the five patients showed FSGS in two children which is consistent with a predominance of HIVAN in the patients with NS or CKF.

Antiretroviral therapy has changed the natural history and epidemiology of kidney disease in HIV infected patients. Several observational studies in adults indicate the beneficial effect of ART in reducing proteinuria and preserving renal function in adults with HIVAN [50-53]. Studies in children are limited, but case reports show dramatic response of HIVAN to ART [54,55]. In ART naive patients, AKI has been reported to carry a sixfold higher risk of in-hospital mortality related to severe immunosuppression, high viremia, and late commencement of ART [46,56]. In the general HIV population emerging studies record renal benefits of ART with reduced incidence of CKD, preservation of renal function or improvement of glomerular function with regular use of ART [57]. In our study ART was given in 70% of patients with a mortality of 14% among patients who received ART compared with the overall in hospital mortality of 44.4%. Three patients commenced ART before onset of kidney disease, two of these patients had evidence of treatment failure. One patient with good immunologic and virologic control developed left renal artery stenosis. The renal artery stenosis may have been an incidental finding, a study in France, however, observed development of left renal artery stenosis in young patients with HIV and good virologic control [58]. Three patients did not receive ART either because they presented before ART became available in our country, or they presented late and died before commencement of ART was possible.

Apart from ART other drugs that have been used in the management of kidney disease in HIV seropositive patients include angiotensin converting enzyme inhibitors (ACEIs) and steroids [10,59]. Case control and cohort studies in adults have indicated ACE inhibitors are associated with delayed progression of HIVAN and long term renal survival in adult patients [35,60-62].However, no prospective studies have been performed to determine the efficacy of ACEIs in children with HIVAN. The benefit of ACEIs may be maximal when it is commenced early in the course of HIVAN before the onset of renal failure [62]. Steroids were not used in any of the patients as evidence of the benefit of steroid therapy in childhood HIVAN is inconclusive [3,10,15].

The in-hospital mortality of 40%, caused mainly by co-morbidities such as septicaemia, and complications of renal failure, highlight the high mortality associated with kidney disease in HIV seropositive children in our study. In the United States of America, HIVAN, especially before ART became widely available, was typically associated with

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and analgesia; and to reduce adverse effects or complications associated with using a high dose of a single drug. Such combinations have additive or synergistic interactions. Anaesthetists are faced with the challenge of finding ideal additives to local anaesthetics to adequately manage pain.

The search for suitable agents to prolong the duration of LA has been on-going for many years. The use of opioids as additives is well established but has potential for adverse effects such as pruritus, nausea, vomiting and delayed respiratory depression [1]. Neostigmine, an anticholinesterase, is one of the non-opioids being used as an additive to LA singly or in combination with opioids or other additives. Neostigmine is a quaternary amine, unable to cross the blood-brain barrier and therefore has to be administered spinally in order to reach the target organ, the spinal cord [2].

Studies indicate that intrathecal cholinesterase inhibitors modulate pain in animals and humans [1,2]. Spinally administered neostigmine causes analgesia in animals and human by preventing the breakdown of synaptically released acetylcholine (ach), which acts on muscarinic and nicotinic receptors in the spinal cord [1]. Intrathecal neostigmine has been shown to produce a long-lasting postoperative analgesia [3] and enhance opioid analgesia in human [4]. Apart from dose-dependent nausea and vomiting, neuraxial neostigmine lacks respiratory depressant effect, no pruritus and sedation making it a favourable agent [3]. This study was therefore undertaken to determine the analgesic and adverse effects provided by addition of a small dose intrathecal neostigmine to bupivacaine and fentanyl in male adults undergoing lower abdominal surgery under spinal anaesthesia. The male subjects were chosen to avoid bias as it has been suggested that oestrogen present in the premenopausal adult female may underlie the greater potency of intrathecal neostigmine in women [5].

Methods and materials

The study protocol was approved by the Joint ethics Committee of University of Ibadan/University College Hospital (UI/UCH), Ibadan. Sixty ASA I-II male adults aged 18 to 65 years scheduled for elective orthopaedic, urologic and general surgical procedures under spinal anaesthesia were studied at the University College Hospital, Ibadan. The patients were randomly allocated into two groups of 30 patients each, using a simple table of randomization: neostigmine and saline groups. The procedure was explained to the patients and an informed consent obtained from each patient.

All study medications were aseptically prepared by an anaesthetist who was blinded to the study groups. Neither the investigators who performed all of the subsequent assessments nor the patients were aware of the study group assignment also. Each patient was fasted overnight and premedicated with oral diazepam (0.5ml) the night before surgery. All patients were preloaded with crystalloids at 15mls/kg twenty minutes before spinal block, followed by 125mls/hr intraoperatively. Spinal puncture was performed at the L_2/L_3 or L_3/L_4 interspace with a 25 or 26G Whitacre needle with the patient in the sitting position. Neostigmine group received 0.5% hyperbaric bupivacaine (Marcaine Heavy 0.5%, AstraZeneca, Sweden)15mg, fentanyl 25μg and preservative-free neostigmine 25μg (Neostigmine Methylsulphate 2.5mg/ml, Hameln Pharmaceuticals, Gmbh, Germany) intrathecally over 20 seconds. Saline group received hyperbaric bupivacaine 15mg, fentanyl 25μg and 0.9% saline 5mls intrathecally. All intrathecal drugs were made to the same volume of 4mls. Patients were positioned supine with 45 degree heads up. The end of spinal injection was taken as time zero (0).

The blood pressure was monitored every 2mins for the first 20 minutes and then 5mins thereafter throughout the surgery. Other parameters monitored included heart rate with the electrocardiogram and oxygen saturation with the pulse oximeter.

The sensory block was tested using ethyl alcohol and the motor block by the Bromage scale at 3, 5, 10, 15, 20 and at the end of surgery. Patients who experienced inadequate analgesia received supplementary analgesia of IV ketorolac 0.5mg/kg and intravenous paracetamol 600mg.

The quality of spinal anaesthesia was judged by the degree of motor and sensory blocks and the need for supplementary intravenous analgesia. Successful spinal block or analgesia was taken as surgical anaesthesia (loss of temperature sensation $\geq T_{10}$ sensory level) and complete motor block of Bromage score 3.

The Visual Analogue Scale was used by the investigators to assess amount of pain every 30 mins intraoperatively. Postoperatively, nurses who have been taught pain assessment tools assessed pain every hour for 12 hours post-spinal injection.

The duration of effective analgesia was measured from the time of drug administration to the time when the VAS pain score was ≥ 5. IV ketorolac 0.5mg/kg and paracetamol 600mg were given for rescue analgesia or when the patient's pain intensity assessment using the VAS was ≥ 5. Total analgesic consumption 12hours postspinal injection was also recorded. The duration of motor block was recorded from the time of drug administration to the time when the patient was able to lift a leg above the mattress (Bromage 0).