INTRODUCTION

High blood pressure (HBP) termed hypertension (HT) consists of having systolic blood pressure (SBP)>140 mmHg and diastolic blood pressure (DBP)>90 mmHg. HT is a silent disease that discreetly claims uncalculated lives each year particularly after 50 years old. Some time ago, HT had been seen as a disease of affluence (DOA) in opposition to malaria or diarrhoea seen as diseases of poverty (DOP). However, current epidemiological studies show that HT strikes both rich and poor populations, leaving no race or social rank excluded. About 15% of the adult population worldwide suffers from the disease which is directly or indirectly responsible for 10 to 20% of all annual deaths. The latest WHO data published in April 2011, hypertension deaths in the world are 7.5 million deaths and the majority of patients are presenting with severe hypertension and in stroke condition showing that many people live with uncontrolled high blood pressure. The management outcome was satisfactory despite some medicines related problems encountered. There is a need to draft best standardized protocols to narrow the quality gap and avoid polypharmacy.

Uncontrolled HBP may lead to severe hypertensive crisis consisting of hypertensive urgencies or emergencies to evaluate the adequacy of treatment regimens and potential drug related problems. Methods: Retrospective/prospective chart review of inpatients admitted for hypertensive crisis at two referral hospitals in Bukavu City, DR Congo. Primary outcomes were decrease in blood pressure, resistance to treatment and death. Results: The profile showed the prevalence of inpatients with hypertensive crisis was 9.7% (169/1848); that included 57% men and 43% women aged 23 to 88 years old whose 55% were on alcohol and tobacco. The majority (46%) had severe hypertension (BP>180/110) including 24.4% emergency cases and 76% emergency cases: the end-organ damages consisted of stroke (32%), heart failure (24.6%), chronic kidney disease (19.7%) associated or not with diabetes (38.9%); Co-morbid conditions were respiratory distress, urinary tract infection, sepsis, malaria, gastritis and cancer. Medication regimens included CCBs, ACEIs and ARBs in multidrug combination with diuretics, beta-blockers and a variety of products for co-existing health conditions. The treatment goal BP<140/90 was achieved in 87% while failure and death occurred in 10.6% and 2.4% respectively. Some drug related problems were encountered. Conclusions: The analysis found that the majority of patients are presenting with severe hypertension and in stroke condition showing that many people live with uncontrolled high blood pressure. The management outcome was satisfactory despite some medicines related problems encountered. There is a need to draft best standardized protocols to narrow the quality gap and avoid polypharmacy.

Key words: Hypertension emergency; hypertensive urgency; management outcomes; drug related problems

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of care and highlight the "quality gap" defined as the difference between present treatment success rates and those thought to be achievable using hypertension best practices described by international societies of hypertension like European Society of Hypertension (ESH) and US National joint committee (NJC).[18,19]

METHODS

Study design and patients

The study consisted on one part of a retrospective analysis of data extracted from patients hospitalized in 2015 in internal medicine services at two referral hospitals in Bukavu city namely 'Hospital provincial de reference de Bukavu' (HPGRB) and 'Hopital general de reference de Panzi' (HGRP). On another part, it consisted of a prospective monitoring of inpatients routinely treated for HE/HU in the two hospitals during the year 2016. Patients were treated at usual without interference of the investigators pharmacists. Data were collected exclusively from patients' medical notes. Pregnant women and patients discharged in 24 hours were excluded for analysis considering that they were not at high risk.

Variables

Age, sex, risk factors, BP levels, comorbidities, symptoms, medications and complaints were collected. HT grade was classified as Stage 0 (SBP=120-139, DBP=80-89 mmHg); Stage 1 (SBP=140-159, DBP=90-99); Stage 2 (SBP=160-179, DBP=100-110); Stage 3 (SBP>180, DBP>110). Therapeutic efficacy meant BP goal<140/90. Drug related problems meant whether patients got a wrong drug for their conditions, received more or less than the dose required, got wrong or no drug taken, experienced adverse drug reaction, or there were manifest or potential drug-drug interactions.

Statistical data analysis

The collected data was analysed with Microsoft Excel Windows and SPSS software v20 for descriptive statistics. Statistical significance of differences between groups, where applicable, was set at p<0.05 using Pearson Fisher’s Test.

RESULTS

Clinical profile of patients

The annual hospital prevalence of HE/HU was 9.7% (189/1948). Table 1 presents patients’ demographics and clinical features. Out of 123 valid cases analysed, there were 71 (57.7%) men vs. 52 (42.3%) women. The majority 59 (48%) were 60-88 years old. About 55.3% were alcohol and/or tobacco users. At the admission, 57.7% presented with BP values higher than 180/110 mmHg (stage-III). For clinical features, 24.4% consisted of HT against 75.6% HE. The signs of EOD were dyspnoea (17.1%), headache, followed by dizziness (55.3%), fatigue (52.8%), palpitation (48%), blurred vision (30.9%), dyspnoea (17.1%), and coma (8.9%). During the treatment, patients complained of vomiting (8.1%), cough (7.3%), fever, lumbar pain, chest pain, diarrhoea or constipation, dehydration, dyspepsia, etc. Those could be either symptoms of co-morbid conditions or drug related side effects. Comorbidities included diabetes (39.9%), urinary infection (15.4%), neonatal and respiratory disorders (14.3%), menorrhagia (4.9%), sepsis (5.7%), cancer (5.6%), and gastritis (6.5%) among others.

Management therapeutic regimens

Table 2 presents examples of antihypertensive regimens in monotherapy or combination of two to five molecules. In total, CCBs were the most used (97%) leaded by amlodipine, followed by ACEIs (52%) and ARBs (3%), diuretics (36%) and beta-blockers (8%). The CCBs included amldipine(Aml), nicardipine(Nic), and nifédipine(NIf). ACEIs and ARBS consisted of enalapril (E), captopril(Cap), and losartan(Los). BBs included atenolol(Ate) and bismolol(Bis). The diuretics used were furosemide(Fur), hydrochlorthiazide(hyd) and spironolactone or Aldactone(Ald).

As shown in the table, various drugs were used depending on the patients. For instance 25 patients received amldipine 10 mg (Aml10); 24 patients received Am5; 9 patients received Cap50. In biotherapy, CCBs were combined with ACEIs (Aml10E5a) or with diuretics (Cap50Fur20), or with BBs (Nic10Bis5). Examples of associating more than two are (Aml10 Cap75 Eno10 Ate100 Fur80).

The antihypertensive medicines were often given in association with antihyperlipidemiantis (atorvastatin), heparin (Eoxanoparine), hemostatics (tranexamic acid), antiplatelets (Clopidogrel), and other cardiovascular agents like atropine, adrenaline, and anticoagulants (Table 3). Besides antihypertensive and other cardiovascular medications described, co-morbidities were managed with a variety of specific pharmacological products in polypharmacy, mainly consisting of antidiabetics (Insulin actrapid or NPH), painkillers (Paracetamol, Tramazol), antimicrobials (Ceftriaxone, ciprofloxacin), antiviral (omeprazol), and respiratory medications (salbutamol), vitamins (C and E), and anticanic (Tamofoxifen). Individual doses fell within the recommended ranges.

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Table 1: Repartition of hypertensive patients by clinical profile in Bukavu referral hospitals

<table>
<thead>
<tr>
<th>Hospitals</th>
<th>Gender</th>
<th>Variables</th>
<th>%</th>
<th>Variables</th>
<th>%</th>
<th>Variables</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPGRB</td>
<td>Female</td>
<td>45.5</td>
<td>23-39</td>
<td>15.4</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HGRP</td>
<td>Male</td>
<td>54.5</td>
<td>40-59</td>
<td>36.6</td>
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<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Disease stage</th>
<th>End-organ damage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0 SBP 120-139</td>
<td>4.1</td>
<td>No</td>
</tr>
<tr>
<td>Alcohol</td>
<td>30.9</td>
<td>1 SBP 140-159</td>
<td>Stroke</td>
</tr>
<tr>
<td>Tobacco</td>
<td>4.1</td>
<td>2 SBP 160-179</td>
<td>Heart Failure</td>
</tr>
<tr>
<td>Both</td>
<td>11.4</td>
<td>3 SBP 180-200</td>
<td>Kidney Disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Complaints</th>
<th>Co-morbidities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Vomiting</td>
<td>8.1</td>
<td>No</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Fever</td>
<td>5.7</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52.8</td>
<td>Urinary Infection</td>
<td></td>
</tr>
<tr>
<td>Palpitation</td>
<td>Chest pain</td>
<td>5.7</td>
<td>Malaria</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>Epigastric pain</td>
<td>5.7</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>17.1</td>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>8.9</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Lung-œdema</td>
<td>4.1</td>
<td>Pneumonia</td>
<td></td>
</tr>
<tr>
<td>Hemiplegic</td>
<td>3.3</td>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td>3.3</td>
<td>Benin Prostate H.</td>
<td></td>
</tr>
<tr>
<td>Ear rings</td>
<td>3.3</td>
<td>Haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Pleurisy</td>
<td>2.4</td>
<td>Dehydration</td>
<td></td>
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<tr>
<td>Epistaxis</td>
<td>2.4</td>
<td>Hepatocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Cardiac asthma</td>
<td>1.6</td>
<td>Polyartralgia</td>
<td></td>
</tr>
<tr>
<td>Leg œdema</td>
<td>1.6</td>
<td>Migraine</td>
<td></td>
</tr>
</tbody>
</table>

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Management outcomes

Figure 1 summarizes BP values at admission (SBPin-DBPin) and at discharge (SBPout-DBPout) time. The treatment success was appreciated by the profile of BP at discharge compared to admission day. The mean ± SD of SBPin was 181.67 ± 29.43 (110-280) compared to SBPout of 123.47 ± 18.76 (65-220). The mean ± SD of DBPin was 107.90 ± 20.24 (60-180) compared to DBPout of 73.54 ± 14.03 (45-140). The difference was statistically significant (p=0.001).

Profile of treatment outcomes in 123 hypertensive inpatients in Bukavu is shown below. The majority of patients present with hypertension stage III (BP>180/110) and hypertensive encephalopathy (4.9%). This is consistent with other studies showing that the most common clinical presentations of HE are stroke (32%), heart failure (14.6%), chronic kidney disease (9.7%), and hypertensive encephalopathy (4.9%).

Effect of regimens on outcomes

Figure 2 presents the curves describing the evolution of treatment during the 6 first days and at the discharge time which varied from day 5 to day 30. We compared CCBs based to ACEIs based regimens. SBP and DBP for CCBs (SBPccb and DBPccb) were compared to SBP and DBP for ACEIs (SBPacei and DBPacei) and to SBP and DBP of multiple associations (SBPmix and DBPmix).

There were no significant differences for patients treated with CCBs and ACEIs even though the decrease was slightly rapid under ACEIs.

DISCUSSION

The proportion of hypertensive inpatients approached 9.7% in the internal medicine services of the two hospitals. The HT prevalence in the entire population of Southern Kivu province has been estimated to 41.4% in urban vs 38.1% in rural areas. The finding in Bukavu shows that many people are living with HT as silent condition and remained ignorant about their status and untreated; they lately rush to hospital in hypertension urgency or emergency episodes. In fact, the majority of patients present with hypertension stage III(BP>180/110) including 24% HU and 76% HE. In a study by Zampaglione et al. done in emergency room, HU accounted for 76% and HE for 24%.

The study sample comprised of 57.7% of men against 42.3% women, with end-organ damages consisting of haemorrhagic or ischemic stroke (32%), heart failure (14.6%), chronic kidney disease (9.7%), and hypertensive encephalopathy (4.9%). This is consistent with other studies showing that the most common clinical presentations of HE are cerebral infarction (24.5%) associated with intracranial haemorrhage, aortic dissection, congestive heart failure and acute myocardial infarction (12%), pulmonary oedema (22.5%) and hypertensive encephalopathy (16.3%).

Disease symptoms included dizziness, fatigue, headache, nosebleed, tachycardia, heart palpitations, blurred vision and ear ringing while the main co-morbidities were diabetes (38.8%), respiratory distress, urinary tract infection, sepsis, malaria, gastritis and cancer.

The study sample comprised of 57.7% of men against 42.3% women, supporting world statistics that show both sexes would be exposed in the same way, whatever the general trends show that men are somehow more exposed than women. The population above 60-88 years old was the most affected by HBP in this study (48%), consistent with many studies showing that HT strikes less than 2% of patients under 20 years and more than 40% of patients over 50 years old. About 50% of patients were alcohol drinkers and tobacco smokers. Alcohol or...
smoking can increase the risk of complications when associated with aging.

The JNC8 recommends reduction of BP levels below 150/90 mm in patients aged 60 years or older, reduction below 140/90 mm Hg in patients younger than 60 years as well as those older than 18 years with either chronic kidney disease (CKD) or diabetes.\textsuperscript{[19]} With the regimens delivered in Bukavu hospitals, the therapeutic goal BP<140/90 was achieved in 87% of patients within 6 to 30 days after the treatment was initiated. Failure and death affected 12.6% and 2.4% respectively within the 30 days of follow-up. Resistant hypertension also is a common clinical problem faced by both primary care clinicians and specialists. While the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants.\textsuperscript{[2]}

The treatment success rate is not too widely different with regard to other studies.\textsuperscript{[29-31]} However, some gap was observed with regard to contemporary recommendations\textsuperscript{[32-35]} applicable to HE/HU management. To manage HEs, labetalol an alpha-beta-blocking agent has proven to be quite beneficial in the treatment of patients as well as fenoldopam, a peripheral dopamine-1-receptor agonist given as initial IV dose of 0.1 µg/kg/min titrated every 15 min. No patient was given labetalol or fenoldopam in this study. In hypertensive encephalopathy,

The preferred medications are labetalol, nicardipine, esmolol. Only nicardipine was used along side other CCBs and ACEIs. Direct vasodilators like nitroprusside and hydralazine are contra-indicated in this case. In general, direct vasodilators were not used in any case.

In acute heart failure, the preferred medications are IV nitroglycerin or sublingual nitroglycerin and IV enalaprilat. Nitrolingual was prescribed in patients with heart failure and pulmonary oedema. One NJC8 recommendation stipulates that regardless of race or diabetes status, in patients 18 years or older with CKD, initial or add-on therapy should consist of an ACE inhibitor or ARB and do not use an ACE inhibitor in conjunction with an ARB in the same patient. In our cases, patients presenting CKF were initiated only on amlodipine or nicardipine. Certain beta blockers and thiazides in combination increase insulin resistance (risk of diabetes) with increased triglycerides and congestive heart failure. Here, only hydrochlorothiazide was used as thiazide but not in combination with BBs. Furosemide (Lasix) which is loop diuretic was preferred to thiazide-type. This is because in the country, the only best known diuretic is Lasix. In hypertension and Angor, CCBs with tachychardisant effect as Amlor LP should be avoided. However Amlor was unfortunately the agent of choice in many patients despite the co-existing cardiac illnesses. In the majority of our patients, the treatment was initiated with amlodipine, nicardipine or enalapril. Alpha-receptor inhibitors are most often prescribed in case of failure of at least two other treatments; centrally acting alpha-2 agonists and direct vasodilators have place in special and emergency episodes. No alpha-1 blockers were indicated in resistant patients and only 1 patient was treated with Moxonidine a central acting conger to clonidine.

Many studies have showed that drug-related problems are prevalent and cause considerable patient morbidity and in some cases death, as well as increased health care expenditures. The common classification of DRPs has a hierarchical structure with six main categories (drug

Figure 1: Profile of treatment outcomes in 123 hypertensive inpatients in Bukavu. BP values at admission (SBPin and DBPin) and at discharge (SBPout and DBPout)

Figure 2: Profile of treatment outcomes in 123 hypertensive inpatients in Bukavu. Evolution of BP values during the first 6 days and at the discharge time for patients successfully treated with CCBs alone, or ACEIs alone or CCBs combined with other drugs.
choice, dosing, adverse drug reaction, interaction, drug use and other) and 12 subcategories. [36,37] For this study, we adopted the structure comprising 8 DRPs and the following observations can be made. DRP1. Inappropriate Medication; the patient takes or receives a drug other than the one required. The result showed that the medications prescribed were drugs of choice in the treatment of all-types hypertension and comorbidities. Diabetes was managed with insulin, glibenclamide and metformin. For malaria, only Artemether/Lumefantrine (CoArtem) was prescribed. Ciprofloxacin and ceftriaxone were the major antibiotics. Proton pump inhibitors like omeprazole, antihistamine-H2 like ranitidine, or antacids like Maalox were used for ulcer management. Some bronchodilators and anti-inflammatory were also prescribed alongside painkillers and anti-anemia drugs in case. Although all medicines used sounded appropriate, it has been however difficult to agree whether all those were needed.

DRP2: the patient needs a drug, but does not receive it. In the majority of cases, patients received their first choice treatment, but in all cases. The following example illustrates the gap. Mr AD, aged 54 years old, presented at the hospital with Grade III hypertension and complicated stroke with intracranial effusion, headache and severe pain. At the entrance BP was 275/178 mmHg. Rx initiated with Nicardipine inj 1x10 mg, Amlodipine 1x10 mg, Atenolol 1x50 mg; at day 4, BP was 170/120 mmHg and received Lasix 2x40 mg, Captopril 3x25 mg, Atenolol 1x50 mg; at day 5, BP was 180/120 mmHg and received the same treatment as day 4; at day 6, BP was 200/120 mmHg and received Captopril 3x25 mg, Nicardipine inj 1x10 mg; at day 7, BP was 180/120 mmHg and received Lasix 2x40 mg, Enalapril 2x5 mg, Atenolol 2x50 mg, Amlodipine 1x10 mg, Captopril 3x25 mg; at day 8 the patient died in a collapse with BP 220/150. At the entrance she received Nicardipine 1x10 mg inj; at day 2: BP was 220/130 mmHg and received again Nicardipine 1x10 mg inj; at day 3 BP dropped to 180/120 mmHg, and received Captopril 3x25 mg, Atenolol 1x50 mg and Amlodipine 1x5 mg; at day 4, BP was 170/120 mmHg and received Lasix 2x40 mg, Captopril 3x25 mg, Atenolol 1x50 mg; at day 5, BP was 180/120 mmHg and received the same treatment as day 4; at day 6, BP was 200/120 mmHg and received Captopril 3x25 mg, Nicardipine inj 1x10 mg; at day 7, BP was 180/120 mmHg and received Lasix 2x40 mg, Enalapril 2x5 mg, Atenolol 2x50 mg, Amlodipine 1x10 mg, Captopril 3x25 mg; at day 8 the patient died in a collapse with BP 65/45 mmHg. This case illustrates wrong use of the recommended ranges. However there was no sign of individual adjustment on the basis of kidney failure. Ms X Age 63 years presented with HTA grade III complicated with Ischemic Stroke. At the entrance the patient had a speech problem, impotence of inferior members, weakness of the legs, and had primary responsibility for final content. All authors read and approved the final manuscript.

DRP3 and DRP4: The patient takes or receives the correct drug, but at too low or too high doses. The standard doses used were in the recommended ranges. However there was no sign of individual adjustment on the basis of kidney failure. Ms X Age 63 years presented with HTA grade III complicated with Ischemic Stroke. At the entrance the patient had a speech problem, impotence of inferior members, weakness of the legs, and had primary responsibility for final content. All authors read and approved the final manuscript.

DRP5: The patient does not take or does not receive the medication as prescribed. Our sample consisted of inpatients in Internal Medicine Service. Therefore, we assumed that the compliance or adherence was excellent because the administration was done by nurses. However, this has not been confirmed since all patients were required to pay cash medicines mostly outside the hospital. The situation is almost similar in many poor countries. Also after exit to home, it is difficult to make a valuable judgment on adherence as the treatment is costly and demanding. Many medicines were prescribed in trade name that are expensive, like Efferalgan (paracetamol), Dafalgan (paracetamol), Largactil (chlorpromazine); Lexotan (bromzapam); Nootropil (piracetam); Cortancyl (prednisone). Diabetaz (glibenclamide), Vermox (mebendazole), Glucophage (metformin), Gilben (glibenclamide), Iproprosec (rabeprazole), Duphalar (lactulose), Uclcar (sucralfate), Spasfon (mebeverine), Clamoxil(amoxicillin), Novadex (tamoxifen), Fefol (iron and folate).

RP6: Adverse reaction. A number of complaints were noticed like cough, diarrhoea, constipation, vomiting, epigastralgia, etc. It was difficult to establish a decisive link between those complaints and the medications received. Nevertheless, coughing is characteristic of ACEI agents; headache and palpitations are associated with CCBs. [38,39]

DRP7: Interactions. The patient undergoes an interaction between the drug and another drug, food, or a biological test. Some possible interactions could occur even though not evidenced in this case. Combination of statins (simvastatin, atorvastatin) and inhibitors of CyP450 3A4 can lead to serious liver and muscle side effects. Aldactone interacts with ACE inhibitors and ARBs (addition of hyperkalaemia effect with doses of 12.5 to 50 mg per day). Their antihypertensive effects may be increased in combination with antipsychotics, tricyclic antidepressants. [40-42]

DRP8: Unnecessary medications. Several cases have been met where the combination of vitamin C and vitamin E or redundancies were systematically given without justification.

CONCLUSIONS

The study revealed high level of hypertensive emergency, high frequency of all-type stroke, diabetes and infections. The medicines used and outcomes were satisfactory despite some drug related problems. However, there is a need to fix best standardized protocols susceptible to further narrow the quality gap. Educational campaign about early blood pressure checking over 50 years is of great importance to reduce the high frequency of stroke observed.

Ethics approval and consent to participate

The protocol of the study was approved by the Research Ethical Committee of the Faculty of Medicine and Pharmacy of the Official University of Bukavu. The consent to participate was Not Applicable.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No external funds.

Author’s contributions

JNK, BB, and JDS designed research; BB and JDS conducted research; JNK, et al.: Hypertensive Urgencies or Emergencies and Co-Morbidities in Bukavu Referral Hospitals: Clinical Profile, Management Regimens, Outcomes and Drug Related Problems. The authors wish to thank the research nurses, medical coordinators and operations staff as well as patients included in this study.

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Journal of Basic and Clinical Pharmacy, Vol 9, Issue 1, Dec-Feb, 2018


