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Cost-Effectiveness Analysis of Oral Hypoglycemics for Type-2 Diabetes Mellitus at a Tertiary Care Hospital, Nepal

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Abstract: An observational follow-up study on 63 newly diagnosed Type-II diabetic patients was conducted at Tribhuvan University Teaching Hospital, a tertiary care centre, Kathmandu, Nepal. The aims of the study were to determine demographics, prescribing patterns, drug costs and to analyze the effectiveness of different hypoglycemic therapies. The effectiveness of glucose control was analyzed by Wilcoxon signed rank test. The majority of patients (31%) fell into the age strata of 50-60 years. A total of 63 prescriptions were screened including anti-diabetics drugs and other drugs. The average number of drugs per prescription sheet was 2.72 ± 2.23. Eighty-two percent (82%) of the patients were recommended oral hypoglycemic agents. The prescribing frequency of biguanides was more than sulphonylureas. Biguanides were prescribed more frequently than sulfonylureas. The biguanide monotherapy group (p = 0.001) and the combination of biguanide and sulfonylureas (p = 0.028) were the most effective treatment methods, and the p-value of fasting blood glucose was the lowest at follow-up. Nearly 55% of patients receiving the combination achieved glucose control. In summary, this study reflects the best treatment for patients with diabetes. Future studies of larger patient populations need to evaluate existing treatment models to ensure good practice and quality of care.

Key words: Diabetes milltus, cost effectiveness analysis, biguanides, sulphonylureas, HbA1C, Nepal.

1. Introduction

Diabetes, commonly known as diabetes mellitus, has been described as a metabolic disease in which people have high blood glucose (hyperglycemia), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both. It is a multi-factorial disease caused by both a genetic factor linked to impaired insulin secretion and insulin resistance and environmental factors such as overweight, lack of exercise, all types of stress, as well as aging. Among the many symptoms, frequent urination, intense thirst and hunger, weight gain, unusual weight loss, fatigue, unhealed wounds and bruises, male sexual dysfunction, numbness and tingling in hands and feet are rare [1].

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Type-2 diabetes is characterized by tissue resistance to insulin and a relative lack of insulin secretion. A particular individual may have more resistance or more B-cell deficiency, and abnormalities may be mild or severe. Although insulin is produced by the B-cells in these patients, it is not sufficient to overcome the resistance and the blood glucose rises. The impaired insulin action also affects fat metabolism, resulting in increased free fatty acid flux and triglyceride levels, and reciprocally low high-density lipoprotein (HDL) levels [2]. Individuals with type-2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control blood glucose. It is likely that 10%-20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and type 2, or have a slowly progressing type 1, and ultimately will require full insulin replacement [3].

In 2017, International Diabetes Federation (IDF) estimated that approximately 425 million adults (20-79

years) were living with diabetes, and by 2045 it will rise to 629 million. 79% of adults with diabetes were between the ages of 40-59 years. The proportion of people with type 2 diabetes is increasing in most countries. Diabetes was the cause of about 4 million deaths worldwide. At least 727 billion USD was spent on diabetes in 2017, which was 12% of the total spending on adults [4].

In Nepal, IDF estimated diabetes prevalence rate of 7.3% in the adult age group of 20-79 year in 2017, with 11,693 diabetes related death. Mean diabetes related expenditure per person with diabetes was estimated to be 20.79 USD. The Nepal Diabetes Association (NDA) reports the prevalence of diabetes in the population of 20 years and above to be 14.65% in urban areas and 2.5% in rural areas [5].

A survey conducted in urban Nepal between 2001 and 2002 showed that 10.8% and 13.2% of males suffered from diabetes and pre-diabetes respectively, while 6.9% and 10.2% (woman) females had diabetes respectively [6]. In TU Teaching Hospital, Kathmandu, diabetes comprised almost 10% of the admissions in the medical ward in 2010. Up to 95% of diabetic patients were reported to be type 2 diabetes [7, 8]. Hence, the burden of type-2 diabetes is enormous worldwide as well as in Nepal.

1.1 Medication Approach to T2DM

There are many kinds of oral hypoglycemic agents on the market, such as biguanides, α-reductase inhibitors, sulphonylureas, etc. Each agent has its peculiarity in mechanism and site of action; thus, their glucose-lowering effects and treatment costs for patients vary significantly [9]. Metformin, a biguanide drug, is the first-line oral hypoglycemic agent for T2DM incompliance with international guide-lines with proven efficacy, safety, and cost-effectiveness [10].

The sulfonylureas and biguanides have been available the longest and are the traditional initial treatment choice for type 2 diabetes. Novel classes of rapidly acting insulin secretagogues, the meglitinides and D-phenylalanine derivatives, are alternatives to the short-acting sulfonylurea, tolbutamide. The thiazolidinediones, under development since the early 1980s, are very effective agents that reduce insulin resistance. α-glucosidase inhibitors have a relatively weak anti-diabetic effect and significant adverse effects, and they are used primarily as adjunctive therapy in individuals who can not achieve their glycemic goals with other medications [11-13].

1.2 An Approach to Pharmaco-Economics

Pharmaco-economics is the branch of health economics that uses cost-benefit, cost-effectiveness, cost-minimization, cost of illness and cost-utility analyses to compare pharmaceutical products and treatment strategies [14]. It is necessary because the rising cost of healthcare delivery systems is a major concern to all patients, healthcare professionals, and the government.

Inside of the health economics the medical costs can be categorized in three ways in terms of measuring of these: distinct direct medical, direct nonmedical and indirect costs. The direct medical costs contain the hospitalization, outpatient visits (to primary care providers and specialists), procedures and tests (blood analysis, ultrasound scans, surgical interventions), medical devices, home care, nursing care and medications. The direct nonmedical costs comprise the transportations, nonmedical services (home helper, meals on wheels, social assistance), devices and investments or informal care. The indirect costs mostly mean the sick leave or absences, reduced productivity at work, early retirement due to illness and premature death [15].

There are four types of economic analyses that can be applied fruitfully to the analysis of drugs: cost minimization, cost-effectiveness, cost-utility and cost-benefit. Each type of analysis compares the costs and therapeutic consequences of different drugs (or other treatments) in treating a particular medical

condition. The 4 types of economic analyses differ primarily in whether therapeutic consequences are measured in monetary terms (CBA), physical units (CEA), or measures of quality of life (CUA), or are assumed equal (CMA).

Cost-effectiveness analysis is appropriate when a single dimension of effectiveness characterizes the relevant outcome for all therapies and competing therapies do not produce an equivalent likelihood of outcomes (i.e. the alternative therapies do not have the same clinical effectiveness). When one drug is clearly superior to another, but less costly, the efficiency decision is easy: choose the drug with greater therapeutic benefit. More commonly, however, the drug that is more effective is also more expensive; in this setting CEA is appropriate. The analysis must describe the "incremental" gain in therapeutic benefits derived from the extra costs and decide whether the extra benefits are worth the extra costs.

The decision rule in CEA is to choose the option that shows the least cost per outcome measure gained (e.g. the least costly means of avoiding an infant death, the cost per year of life gained, etc.). In CEA, analytical results are summarized by the ratio of cost to effectiveness (C/E) [16].

In this study cost effectiveness analysis is only used. It evaluates the cost differences between two or more medications from one group and with a similar clinical effect. Result of cost effectiveness analysis is expressed as an average cost-effectiveness ratio (ACER) or as incremental cost effectiveness ratio (ICER). ACER/ICER = healthcare cost divided by clinical outcome/benefit [16].

Because of its chronicity, of the seriousness of its complications and of the resources that must be used to fight it, diabetes is a very expensive disease not only for the patient and the family, but also for the states' system of health. The overall costs of diabetes to the health care system and society depend on its prevalence, in addition to the severity, type of drug used, and compliance to medications by the patients and development as well as progression of complications.

Since diabetes is one of the most prevalent chronic diseases of Nepal and a significant part of the healthcare economy is utilized in its management, the current study is aimed at finding out which model of therapy could be the most cost-effective in type-2 DM without compromising in its quality, so that the economic burden on the patient can be reduced. Throughout our literature search, we did not come across any similar study on costly implications of diabetes locally, making the study more desirable. Hence, the aims of the study are to determine the demographics, prescribing patterns, drug cost and analyze the effectiveness of different therapies.

2. Materials and Methods

2.1 Study Design

It is an observational prospective study, where 63 patients were enrolled for the study over 3 months from July to August 2017.

2.2 Study Site

Study site is diabetes counseling center of TUTH, where the out-patients are referred for counseling. TUTH is one of the largest hospitals of Nepal and is a tertiary health care center. The study site is convenient because of its good patient flow.

2.3 Sample Population

Sample population is out-patients of the TUTH visiting the diabetes counseling center of TUTH.

2.4 Inclusion Criteria

(1) Newly detected cases of type-2 diabetes of OPD and follow up within a span of 3 months ± 15 days;

(2) Patients receiving an oral hypoglycemic or a combination;

(3) Both genders;

(4) Age between 18 and 80 years;

(5) Patients with co-morbid conditions such as

hypertension, dyslipidemia, hypothyroidism, coronary artery disease and myocardial infarction;

(6) Patients responsible for taking their own medication;

(7) Patients that are ambulatory (non-institutionalized);

(8) Patients that can communicate in English or Nepali (both written and oral).

2.5 Exclusion Criteria

(1) Patients with no appropriate laboratory report and proper medication chart shall be excluded;

(2) Patients with type 1 diabetes;

(3) Patients with gestational diabetes;

(4) Patients with cognitive impairments.

2.6 Sample Size

The study was conducted with purposive sampling, in which all the patients who meet the inclusion criteria, were enrolled in the study within the given time frame. Thus, a total of 63 patients were taken into the study who fall into that criteria.

2.7 Study Variables

(1) Age range;

(2) Sex;

(3) Marital status;

(4) Occupation;

(5) Prevalence of other co-morbidities;

(6) Mean of drugs per prescription;

(7) No. of drugs prescribed in generic name;

(8) Initial treatment approach;

(9) Frequency of individual oral hypoglycemic drugs;

(10) Most frequent brand of oral hypoglycemic and their price;

(11) Other groups of drugs prescribed;

(12) Blood glucose level before and after the treatment of 3 months;

(13) HbA1C level before and after the treatment of 3 months;

(14) Drug cost effectiveness analysis.

Effectiveness of drug therapy for different treatment regimens was evaluated in follow-up cases achieving glycemic control i.e. fasting blood glucose (FBG) < 130 mg/dL [12]. This was done from FBG values obtained at the time of diagnosis (FBG I) and at the end of 3 months ± 15 days (FBG II) for each patient by analyzing them statistically by Wilcoxon signed-rank test. The most effective treatment group considered was the one in which a maximum number of patients achieved glycemic control.

Costs of drugs (maximum retail price-MRP) shall be obtained from NiDs, January 2015 edition. Drug acquisition costs (cost of buying a drug) were calculated using the cost of the cheapest and the most expensive available preparation and for the most commonly prescribed dose after converting into Nepalese currency. For the prescribed oral anti-diabetic drugs, cost price determined daily dose and then for a period of 3 months.

Cost effectiveness analysis was done by obtaining incremental cost-effectiveness ratio (ICER) for a period of 3 months. This ratio assesses the net incremental cost of gaining an incremental health benefit over another therapy. In this study a comparison was made between the two most effective treatment modalities.

ICER was obtained using the following formula:

ICER = [Cost of Drug A – Cost of Drug B] ÷ [(FBG IA – FBG IIA) – (FBG IB – FBG IIB)]

where, A = most effective therapy, B = 2nd most effective therapy.

Prescription sheets, laboratory reports, interview and data collection forms were used as data collection tools. The study was undertaken according to the ethical guidelines of the institution and approved by Institutional Ethics Committee; and the patients were undertaken for observation only after their informed consent.

2.8 Data Analysis

Data were tabulated and entered in Microsoft Excel. Analysis was done with the help of Statistical Package SPSS version 20. The distribution of the data was tested for normality using the Shapiro-Wilk test. Then Wilcoxon Signed rank test was applied for testing blood test data for significant change in FBG and Hb1AC levels compared to different oral hypoglycemic groups.

3. Results

A total of 63 newly diagnosed patients of diabetes mellitus were enrolled in the study, out of which 58.7% were males (n = 37), and 41.3% were females (n = 26). Approximately 31% (n = 20) of patients fell in the age group between 50-60 years. Similarly, almost 23% (n = 15), 21% (n = 14) and 18% (n = 12) of the patients fell in the age groups between 40-50 years, 30-40 years and 60-70 years respectively. Each patient falling in the age groups 20-30 years and 70-80 years was also observed.

Co-morbid diseases were found in 37 (58.71%) patients. Hypertension was present in 57 cases (45.3%) of patients among them, it being the most common co-morbidity followed by dyslipidemia (n = 6, 11.3%) and gout disease (n = 5, 9.4%) shown in Fig. 1.

The initial treatment approach for the newly diagnosed patients was found to be diet only, diet with oral hypoglycemic and insulin therapy with diet and oral hypoglycemics. Diet includes the diet regimen by the dietician including lifestyle management with no smoking and no alcohol, as well as exercise advice given as per the BMI of the patients. Among them, for almost 81% (n = 51) the chosen regimen was diet with oral hypoglycemic, followed by diet only for 17.5% (n = 11).

After 3 months ± 15 days, the FBG level was observed to be controlled (< 130 mg/dL) for 27.2% (n = 8) for diet only cases and 52.9% (n = 27) for diet with oral hypoglycemic cases. Only one case for insulin therapy was observed and its after treatment FBG level was controlled (Fig. 2).

A total of 63 numbers of prescriptions were screened and the total number of drugs was found to be 169. Of these 52 drugs were hypoglycemics. Amongst these, biguanides (metformin) were the most frequently (46.9%) prescribed. The mean ± SD of drugs per prescription was 2.72 ± 2.29 (range = 1-9 drugs), with 38.7% (n = 24) of patients receiving 2 drugs or less. Out of the total number of prescriptions, generic prescribing was done in n = 35 prescriptions. Metformin was prescribed in generic name for n = 23 (76.67%).

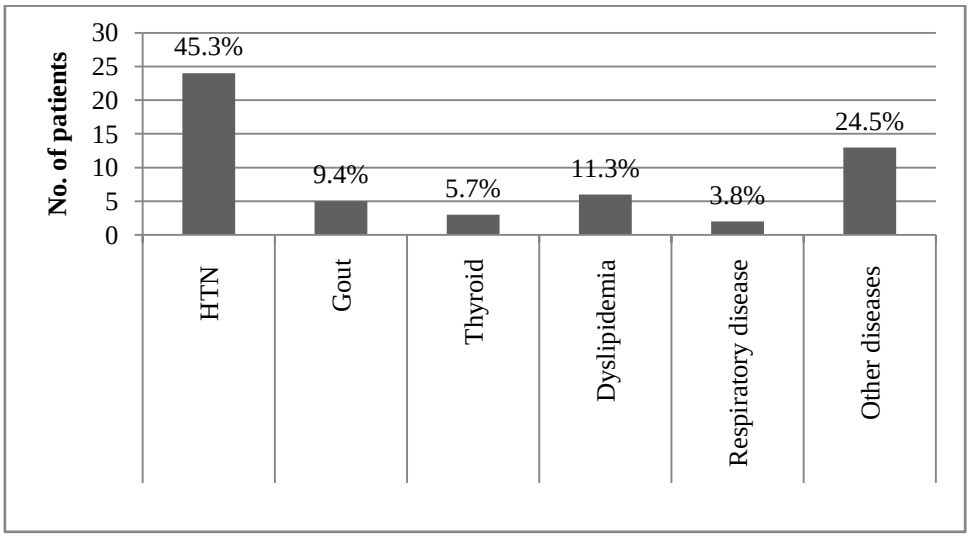
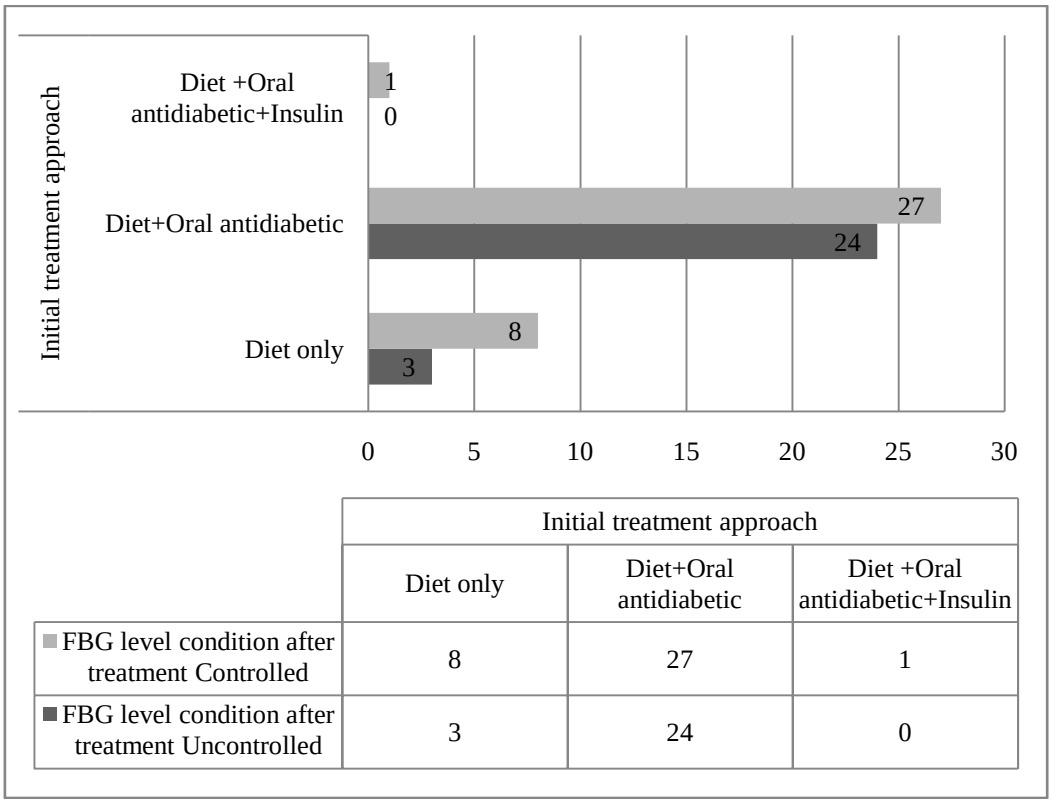


Fig. 1 Co-morbidities associated with patients.



	Initial treatment approach		
	Diet only	Diet+Oral antidiabetic	Diet +Oral antidiabetic+Insulin
FBG level condition after treatment Controlled	8	27	1
FBG level condition after treatment Uncontrolled	3	24	0

Fig. 2 Effect of initial treatment approach in FBG level condition of patients.

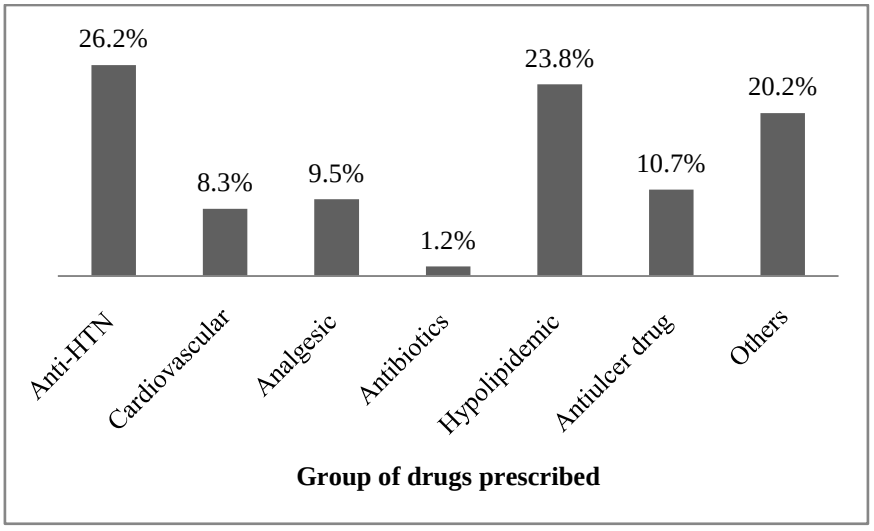


Fig. 3 Group of anti-diabetic drugs prescribed.

The most frequently prescribed antidiabetic drug was found to be biguanide (metformin) (46.9%) followed by combination by metformin and sulfonylureas (17.2%). Combination of metformin and sitagliptin was prescribed in 9.4%.

Since hypertension was the most prevalent co-morbid disease, the group of antihypertensive drugs was most frequently prescribed at 26.2% concomitantly with anti-diabetics. They were followed by hypo-lipidemic which were prescribed in 23.8% of patients. Other groups of drugs prescribed include antihistamine, anti-helminthic, vitamin, antiepileptic, laxative, antithyroid and bronchodilator (Fig. 3).

The mostly prescribed brand of metformin was

found to be Effimet (Suswathya) which was given to 15.4% of the patients taking oral hypoglycemic. Zoryl (Intas) was prescribed for the same percentage. Other popular brands were found to be Glycomet (USV), Formin (Lapen), Siptin (Quest) and Glyfall, all whose percentage of prescription was 11.5%. Other brands of metformin that were minorly prescribed were Oblicheck, Metfor, Glyciphage, and Diamet (Fig. 4).

The MRPs of mostly prescribed brands of oral hypoglycemic were collected and the price variation was observed as shown in Fig. 5. The cheapest brands were found to be of metformin while the most expensive preparations are those of sitagliptins.

The total number of patients whose FBG level was controlled after treatment was found to be 57.1% and those whose Hb1AC level was controlled was 50.8%. And 53.3% of patients using metformin were found to have controlled blood levels and 54.5% of them using a combination of metformin and SU were found to have controlled levels (Figs. 6 and 7). Thus, combination of metformin and SU was found to be more effective than metformin alone.

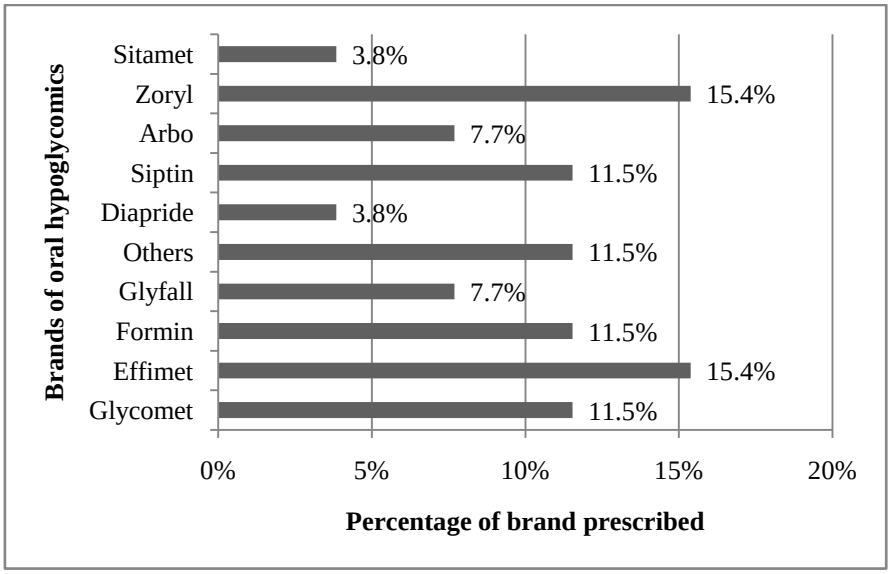


Fig. 4 Different brands of oral hypoglycemic drugs prescribed.

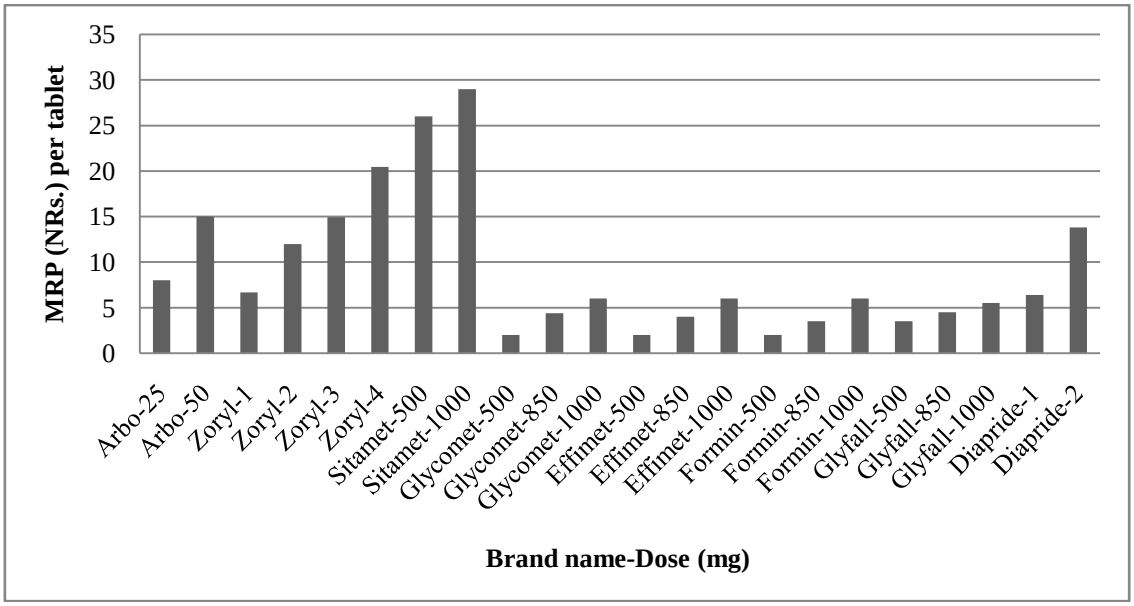


Fig. 5 Cost-variation of different brands of oral hypoglycemic drugs.

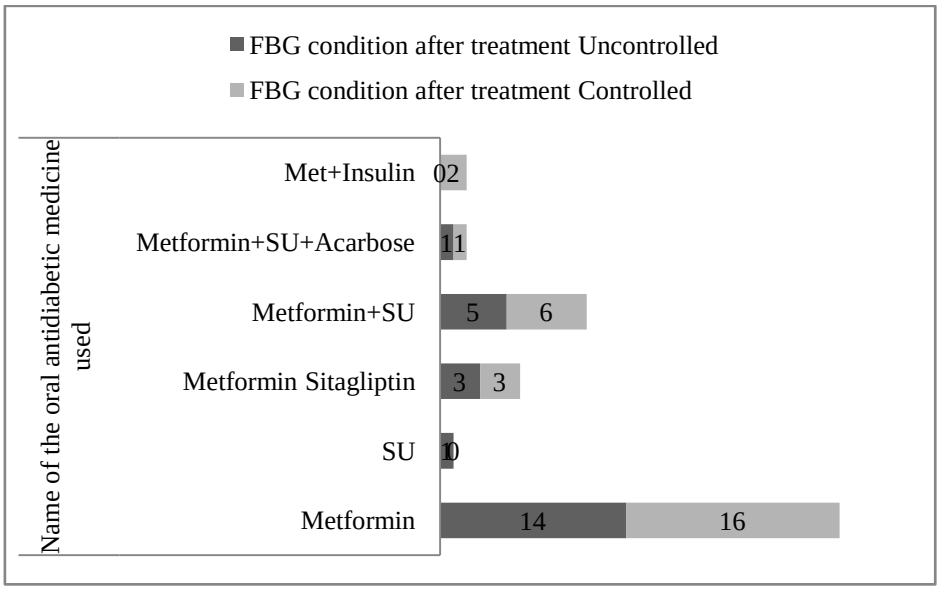


Fig. 6 FBG level condition before and after treatment.

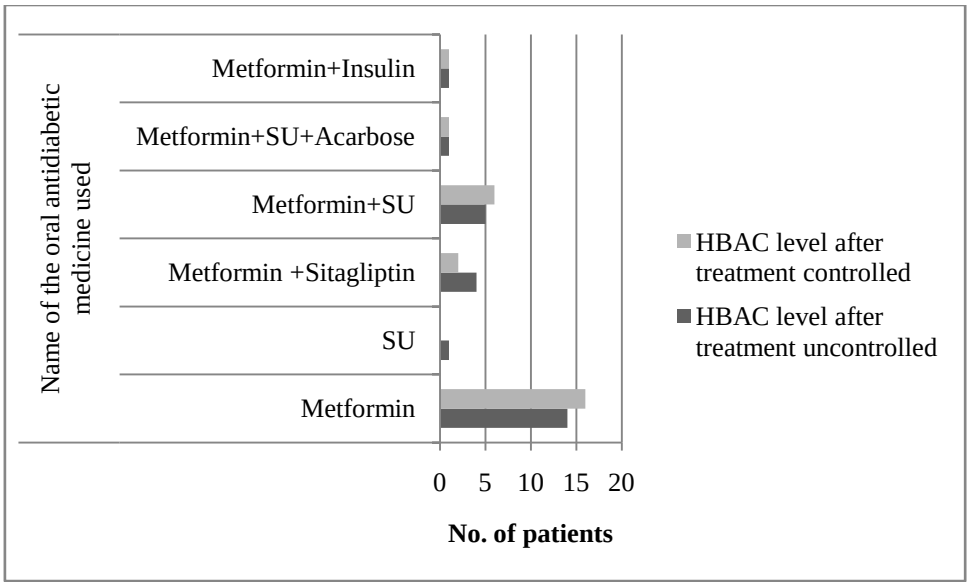


Fig. 7 HbA1C level condition before and after treatment.

The mean FBG level before and after the treatment of the total patients was found to be 158.52 ± 5.3 mg/dL and 129.35 ± 4.02 mg/dL respectively. The mean Hb1AC level and FBG level before and after the treatment of the total patients was found to be 8.42% ± 0.19% and 7.02% ± 0.16% respectively (Table 1).

The FBG level and Hb1AC level before and after treatment were tested for normality using the Shapiro-Wilk test. The *p*-value was less than 0.01, hence, the null hypothesis of the data not being normally distribution is accepted. Since the data are not normally distributed data, non-parametric test, Wilcoxon signed rank test was used.

The *p*-value of FBG levels for biguanides only group was 0.001 and for combination of biguanides + sulfonylureas group was 0.028 which is highly significant. Therefore, it was noted that these were the highly effective therapeutic modalities. As the numbers of patients in other drug group combinations were small, their analysis was not done. Further it can be seen that the combination therapy of metformin and sulfonylurea was the most effective pharmacological

Table 1 Mean FBG and HbA1C level before and after treatment.

Drug used	Mean FBG level (mg/dL) ± S.E.		Mean HB1AC level (%) ± S.E.	
	Before treatment	After treatment	Before treatment	After treatment
Metformin	155.34 (± 34.25)	130.33 (± 32.69)	8.16 (± 0.97)	6.9 (± 0.95)
Metformin + Sitagliptin	191.73 (± 21.79)	144.96 (± 17.74)	9.65 (± 0.71)	7.9 (± 0.79)
Metformin + SU	187.69 (± 14.99)	137.34 (± 10.11)	9.5 (± 0.66)	7.4 (± 0.55)
Total	158.52 (± 5.32)	129.35 (± 4.02)	8.4 (± 0.19)	7.02 (± 0.16)

Table 2 Effectiveness analysis of oral hypoglycemic agents.

Treatment	Patients with FBG II < 130 mg/dL (%)	Cost price (MRP) for 3 months therapy (NRs.)	Median (IQR) values of FBG I [X]	Median (IQR) values of FBG II [Y]	X-Y	*p*-value
Metformin	53.31	360	131.89	106.16	25.73	0.01*
Metformin + SU	54.51	601.2	170.13	112.83	57.3	0.028*
Metformin + Sitagliptin	50%	2,340	145.33	112.86	32.47	0.109

* Significant.

treatment regimen among the patients under study, with 54.5% achieving glycemic control followed by biguanides (metformin) only therapy (Table 2).

Finally, ICER = [Cost of Drug A – Cost of Drug B] ÷ [(FBG IA – FBG IIA) – (FBG IB – FBG IIB)].

where, A = Metformin + sulfonylurea combination therapy and, B = Metformin only therapy.

ICER = [601.2–360] ÷ [(170.13–112.83) – (131.89 – 106.16)]

= 241.2 ÷ [57.3–25.73] = 241.2 ÷ 31.57 = 7.64 mg/dL

Therefore, ICER = NRs. 7.64 per mg/dL decrease in blood glucose (i.e. an increased cost of minimum ~NRs. 8/- is required for every 1 mg/dL decrease in fasting blood glucose levels).

4. Discussion and Conclusion

A diabetes mellitus epidemic is underway. It is a chronic disease requiring lifelong treatment. Although lifestyle changes remain the cornerstone of diabetes management, individually they are often insufficient to enable patients to maintain normal blood glucose levels. Pharmacological therapy therefore forms an integral component in the management of diabetes mellitus.

Our study of cost effectiveness analysis of oral hypoglycemic agents showed that ICER of combination of sulfonylurea urea and metformin to metformin alone = NRs. 7.64 per mg/dL decrease in blood glucose, i.e. an increased cost of minimum ~NRs. 8/- is required for every 1 mg/dL decrease in fasting blood glucose levels.

Among the newly diagnosed type-2 diabetic patients, approximately 59% were men and the remaining 41% were women. It was found that most of the patients (31%) were between the age group 50-60. This is consistent with data given by the WHO, which states that in the developing countries, the most frequently affected are in the middle productive years of their lives. With this age group bearing the burden of diabetes, there is a natural adverse effect on the quality of life of the patients and their family members. This may have a major implication in such nations, as the disease is often associated with loss of productivity, causing socioeconomic and psychological setbacks.

Almost 59% of the patients enrolled in the study were associated with co-morbid disease. Out of them almost 46% of the patients had hypertension, suggesting correlation among diabetes and hypertension.

The average number of drugs per prescription is an important index of the scope for review and educational intervention in prescribing practices. By

and large, it is difficult to keep the mean number of drugs per prescription below two, but higher figures always ought to be justified, because of the increased risk of drug interactions and errors of prescribing. Besides polypharmacy is often associated with higher cost, increased side effects and non-compliance. In this study, the mean number of drugs per prescription was found to be 2.72 ± 2.29, which may be considered as minimal. This result is greater than the result obtained in BPKIHS hospital, i.e. 1.83 ± 1.31. A study conducted in Pokhara, Nepal however showed slightly higher values of 3.76 [17].

Studies conducted in South Africa, the US and India during the late 1990s have reported sulphonyl urea as the most frequently prescribed anti-diabetic agent. However prescribing trends have been changing as reported by more recent studies around the world that show metformin as the most commonly prescribed drug. In this study too, biguanides (metformin) was most frequently prescribed (47%). This pattern is consistent with the current treatment algorithm for type-2 DM from the American Diabetes Association and the European Association for the Study of Diabetes, which suggest that metformin should be started along with lifestyle recommendations at the time of diagnosis. Metformin is the best first option at present due to its efficacy, weight reducing effect, cost and low incidence of adverse effects. Sulfonylureas remain the best choice for combination with metformin although their effectiveness on glucose control decreases with time more rapidly.

Out of the total number of prescriptions screened, 30.76% of the drugs prescribed were anti-diabetics. It was also found that about 26% of the drugs prescribed in the total number of drugs were antihypertensive. This finding is further supported by the fact that cardiovascular disease was the most common co-morbidity found in the patients at the time of diagnosis, with hypertension. Similar reports were from studies in Nepal, Germany and Belgium. It must be noted that metformin was prescribed in generic name in about 77%. The study of brands revealed that Effimet and Zoryl are the mostly prescribed brands which were used in almost 15% each.

The most effective oral hypoglycemic was found to be a combination of metformin and sulfonylureas followed by metformin, with reference to fasting blood glucose level. The *p*-value of FBG levels for biguanides only group was 0.01 and for combination of biguanides + sulphonylurea group was 0.028 which are highly significant as found by Wilcoxon signed rank test. The glycemic control was found in only about 57%. The result is in concordance with the study done in Dharan, i.e. the biguanides only group ($p = 0.002$) and combination therapy of biguanides and sulfonylureas group ($p = 0.005$) were the highly effective therapies, as their *p* values of fasting blood glucose levels on follow up were the lowest. In the same study, only 67 patients followed up for 3 months ± 15 days, of which 46 achieved glycemic control. Decreased number of glycemic patients in our study may be since only those patients who followed up were enrolled in our study.

Randomized controlled clinical trials traditionally provided information on drug safety and efficacy. However, drug utilization patterns and clinical effectiveness in a “real world” setting may differ substantially from the data provided from such trials. Most often, clinical effectiveness is influenced by prescriber agent selection and therapy changes, as well as patient adherence with the drug regimen. In this study, a combination of biguanides and sulfonylureas was found to be most effective, with glycemic control (FBG < 130 mg/dL). A surprising observation is that a large percent of patients on diet alone (~72%) achieved glycemic control. This is likely to occur, as the population chosen for diet therapy had less severe hyperglycemia and is consistent with standard clinical practice decisions. However, efficacy of diet therapy itself can not be ruled out.

5. Limitation

This study was limited to an academic practice that may differ from community practice settings. Besides the prospective data sample is small and duration of follow up is short. However, this study can form a basis for future studies with larger number of patients followed up for a longer duration of time which will be reflective of a full population. Including compliance check will strengthen the study even more.

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