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Assessment of Prescribing Pattern of Anti Hypertensive Drugs in Pregnancy and Incidence of Pregnancy Induced Hypertension – A Prospective Study in A South Indian Hospital

KEYWORDS: pregnancy, antenatal care, Pregnancy induced hypertension (PIH), anti hypertensives, Out patient department(OPD).

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ABSTRACT ***Aim:*** *To assess the use of antihypertensive drugs in pregnancy and to determine the incidence of pregnancy induced hypertension.*

Method*: A prospective study was conducted in pregnant women attending antenatal clinic, they were screened for hypertension and the utilization of antihypertensive drugs in pregnancy was evaluated.*

Results*: A total of 300 pregnant women were diagnosed with hypertension. The mean maternal age was 38.54 ± 4.28 years .The prevalence of Preeclampsia, gestational hypertension, chronic hypertension, and eclampsia were 162, 70, 22 and 46 respectively. Highest incidence of hypertension occurred in 21-25 years (39.3%) observed in 111(37.1%) patients of secondary gravida, 160(53.3%) patients were on combination therapy whereas 140(46.6%) were on Monotherapy.*

Conclusion*: Methyldopa was the commonest prescribed antihypertensive in monotherapy and combination, as it is safest during pregnancy.*

INTRODUCTION

Hypertension is the most common medical problem observed during pregnancy as a cause of maternal and fetal morbidity and mortality[1], it complicates almost 10% of all pregnancies[2]. Pregnancies complicated by hypertension are associated with increased risk of adverse fetal, neonatal and maternal outcomes, including preterm birth, intrauterine growth restriction (IUGR), perinatal death, acute renal or hepatic failure, ante partum hemorrhage, postpartum hemorrhage and also leads to maternal death[3].

Hypertensive disorders during pregnancy are classified into 4 categories, as recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy: 1) chronic hypertension, 2) preeclampsia-eclampsia, 3) preeclampsia superimposed on chronic hypertension, and 4) gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy)[4]. In a multicenter study, approximately 30% of hypertensive disorders of pregnancy were due to chronic hypertension while 70% of the cases were diagnosed as gestational hypertension/ pre eclampsia[5].

Treating hypertension will not alter the progression of disease but early treatment not only decreases the frequency of hypertensive crisis, but also the rate of neonatal complications as drugs play an important role in improving human health and promoting well-being. Therefore judicious use of drugs, adequate knowledge, positive approach and awareness towards the drug use are mandatory prerequisites for good maternal and child health[6]. The identification of a drug's teratogenic potential is important because drug-associated malformations are largely preventable. Two important factors to consider when assessing the teratogenic potential of a medication are the stage of pregnancy at which the exposure occurred and the amount of medication taken [7]. Antihypertensive medications are mainly used to prevent or treat severe hypertension, to prolong pregnancy thereby maximizing the gestational age of the infant, and minimizing fetal exposure to medications that may lead to adverse effects. During pregnancy, the use of antihypertensive medications and what level of blood pressure is to be targeted is a challenge. The antihypertensive drugs that are considered safe in pregnancy are methyldopa, beta blockers, calcium channel blockers and vasodilators. Methyldopa is widely used since many years due to its safety, efficacy during pregnancy and less fetal harm. Literature supports the safety and efficacy of Nifedipine and Atenolol used in essential hypertension in pregnancy[8].

Antihypertensive drugs used during pregnancy are relatively common and increasing day by day. The wide range of drugs used during pregnancy includes medications considered contraindicated during pregnancy. The US Food and Drug Administration (FDA) demonstrate safety and efficacy of any drug, before it is marketed. However, Pregnant women are generally excluded from clinical trials on ethical grounds and results related to effect of drug on pregnant animals cannot always be extrapolated in human population [9]. Regardless of the limited information on the safety of drugs in pregnancy, drug use in pregnancy is common [10,11] .The choice of antihypertensive agent is less complex as a small proportion of these drugs have been evaluated in pregnant women and many are found contraindicated[12]. The present study focused on the antihypertensive drug

Volume : 6 | Issue : 9 | September 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

utilization pattern in women attending the antenatal clinic of obstetrics and gynecology department in a tertiary care teaching hospital.

MATERIALS AND METHODS

Study Period: The study was conducted over a period of 1year from November 2013 to February 2014.

Study Design: Pharmacoepidemological studies can help in minimizing the inherent risk of drug use in

Pregnancy by establishing a profile of drug consumption, by evaluating the existing health services and

by investigating the interventional measures[13] . The present cross-sectional study was conducted in

Antenatal Out Patient Department of Obstetrics and Gynecology of Owaisi Hospital and Research Centre,

Princess Esra Hospital (Owaisi Group of Hospitals) and Maternal Health and Research Trust (MHRT),

Hyderabad to evaluate the Drug utilization pattern of anti hypertensives during pregnancy.

Ethics Committee Approval: The Institutional ethics committee permission was taken on 22nd January, 2014 and Written Informed consent was obtained from all the pregnant women before their prescriptions were analysed.

Prescribing Practices: Pregnant women attending the OPD are examined by a team of physicians, professors, lecturers and house surgeons which are part of the unit and are given hand-written prescriptions on OPD case paper to the pregnant women. There is no facility to maintain pregnant women's health records electronically. Pregnant women receive the drugs prescribed to them either from hospital pharmacy if available, free of cost under Arogyasri Scheme or they need to purchase it from a medical store.

Patient Enrolment: Pregnant women were enrolled only after obtaining written informed consent.

Patient Data Collection Form: The demographic profiles of pregnant women along with parity, present and past history of associated medical, surgical, gynaecological and obstetrical illness, number of drugs prescribed per prescription, generic/brand names, drug dose, dosage form, frequency, duration of treatment were collected, sorted and classified in accordance with US FDA risk classification for pregnancy and the detailed information on the prescription records given in the past and at the time of enrolment documented in OPD case paper were recorded on the case record form.

Inclusion criteria: All pregnant Women were enrolled via convenience sampling, in any trimester, attending antenatal outpatient department greater than or equal to 16yrs of age, with or without co-morbidities, were screened for hypertension and patients diagnosed with hypertensive disorder of pregnancy were taken for primary evaluation. Anti hypertensive drug written on the OPD case paper and pregnant women presented with hypertensive disorder were included in the study.

Exclusion criteria: Pregnant women diagnosed with acute and chronic medical conditions other than Hypertensive disorders requiring hospitalization were excluded from the study.

Statistical Analysis: Statistical analysis was done by using descriptive statistics. Data was collected, tabulated and graphs were designed in Excel-2007. Continuous variables were presented as mean values ± Standard Deviation (SD) and categorical variables were presented as percentages.

RESULTS

During one year study, 365 pregnant women visited the OGD, out of which 52 patients did not agree to give informed consent and 13 of them opted for MTP. Though 319 patients were diagnosed with hypertension only 300 of them included in the study. The mean maternal age at delivery was 38.54 ± 4.28 years(Range 16-45 years) as illustrated in Table 1 where as Table 2 provides information on patients characteristics pertaining to study population. Total distributions of patients with respect to age group shows that highest number of patients was found in the age group of 21-25 years (39.3 %) and least was 41-45 years age group (3.6%) as shown in Table 3 and Figure 1. A total of 111 (37.1%) pregnant women were of secondary gravida accounting for the highest followed by 98(32.6) of primi gravida and 91(30.3) of multi gravida as illustrated in Table 4 and Figure 2 . Majority of women 132 (44%) were in the second trimester as shown in Table 5 and Figure 3. 101(33.6) pregnant women were of gestational age between 31-35 weeks accounting for the highest as illustrated in Table 6 and Figure 4. Peripheral edema was the commonest symptom noticed in 43 (33.5) hypertensive pregnant women as depicted in Table 7 and Figure 5.

Prescription Details: A total of 300 prescriptions were analyzed in which 2803 were the total no. of drugs prescribed. The average drugs per prescription were found to be 8.25 **(2-14).** The highest number of drugs prescribed was 16 and the lowest was 3-4 per prescription depending on the condition of the patient. In our study it was noticed that methyldopa for pregnancy induced hypertension, atenolol for known case of hypertension was prescribed commonly. Alone hypertensive drugs were taken into account and it was noticed that monotherapy was followed in 140(46.6%) and combination therapy accounted for 160 (53.3%) of patients as shown in Table 8 and Figure 6, correspondingly the different drugs used in combination therapy are depicted in Table 9 and Figure 7 simultaneously showing the drugs prescribed in both monotherapy and combination therapy together illustrated in Table 10.

DISCUSSION

Hypertensive disorders of pregnancy are considered to be a major worldwide health problem running an increased risk of Perinatal and maternal mortality[1] . The prevalence of Hypertensive Disorder in Pregnancy varies according to geographic regions of world and ranges from 1.5% in Sweden's to 7.5% in Brazil[14] . According to our study, the frequency of hypertensive disorders of pregnancy was 7.8%. The variations can be attributed to racial differences, socioeconomic status and some other parameters like parity and age.

The distribution of different hypertensive disorders of pregnancy was that, Gestational hypertension of pregnancy was diagnosed in 70 (23.3%) cases. 162 patients (54%) and 46 (15.3%) patients appeared to be pre-eclamptic and eclamptic respectively. In India, the incidence of preeclampsia is reported to be 8-10% of the pregnancies[15] . Chronic hypertension was found in 22 (7.33 %) patients in our study. The frequency of chronic hypertension in Iran was

Volume : 6 | Issue : 9 | September 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

0.17% which is similar to our study (0.15 %)[16].

Age has an important influence on the incidence of hypertensive disorders of pregnancy. Young primigravidae under 20 years and all patients over 30 years have an increased chance of hypertension[17]. In our study highest incidence of the hypertensive disorders occurred among those aged 21 to 25 years. This could be because the majority of conceptions take place in this age group in our country. The age distribution of eclampsia patients in our study is similar to other reports and suggests that eclampsia is, probably, a disease of young women[18]. Preeclampsia is more frequent in patients more than 18 years of age and older than 35[19]. In our study majority of preeclampsia patients were between the ages of 18 to 35 years. Preeclampsia and eclampsia were apparently higher in younger pregnant women (less than 30 years) as Yucesoy et al, showed in their recent investigation. The frequency of chronic hypertension appears to be higher in woman aged ≥30[16] years & our study indicates the same

The incidence of PIH is distributed unevenly throughout late gestation, increasing with advancing gestation. Approximately half of PIH cases occur at term (≥37 weeks' gestation), including most cases of gestational hypertension. Early-onset PIH is often associated with severe preeclampsia[20]. The mean gestational age at presentation was 30.4 weeks which is comparable with other study (i.e. 37 weeks). The reported gestational age of onset of preeclampsia is more than 20th week of pregnancy in vast majority of patients, but recently a case was reported from Japan with typical features of preeclampsia occurring at less than 20th weeks of gestation[21].

Preeclampsia is primarily regarded as a disease of first pregnancy. In our study,32.6 % were primi gravidas, 37.1% of secondary gravid and 30.3 % were multi gravidas. Several other authors have reported primi 32.6 parity in 52-73% patients of preeclampsia

.In our study, both primi gravida and secondary gravida were affected more than multi gravidians with eclampsia. But literature indicates that eclampsia is a disease of primigravida. According to Hellman incidence of eclampsia in primigravida and multigravida was in the proportion of 3:1[22].

Oedema was seen in 33.5 % of our patients. Oedema is a very common manifestation seen in upto 80%of normal pregnancies[23].Prevalence of peripheral edema was significantly less than expected and such patients were taken for emergency Lscs for safe confinement.

Anti hypertensives are agents that lower blood pressure. The aim of antihypertensive therapy in the management of pregnancy induced hypertension is to prevent complications for safety of both mother and baby. Monotherapy and combination therapy were used in our hospital for treating hypertension during pregnancies. The most commonly prescribed antihypertensive agent was adrenergic receptor alpha-2 agonists: Methyldopa, Nefidipine, Labetol.The use of combination antihypertensive pharmacotherapy suggests increased Severity of illness where optimal BP control cannot be achieved on monotherapy. The present study reveals that adrenergic receptor alpha-2 agonists(Methyldopa) were mostly prescribed single drug therapy .In the present study, two drug combinations were mostly prescribed (nefidipine+methyldopa-32%,methyldopa+labetalol-8%,nefidipine+labetalol-9%,atenolol+nefidipine 5%,nefidipine+furosemide-2%,methyldopa+furosemide-1%) followed by three drug combinations(labetalol+nefidipin e+methyldopa-9%).In the present study also most of the cases of PIH were treated using Methyldopa or Nifedipine. Methyldopa was the commonest prescribed antihypertensive as monotherapy as well as in combination therapy. Similarly in a study by Cvijic Met.al[24], Methyldopa was most commonly prescribed antihypertensive drugs in 27.8% of patients. In contrast to this, studies from Ray JG et.al[25] showed that Nifedipine (47.7%) was prescribed more frequently than Methyldopa (27.7%).This shows that utilization pattern differ from hospitals, prescribers and among countries also.

In our study, calcium supplements, iron preparations, nutritional supplement, folic-acid and Vitamins, the most frequently used drugs in pregnancy. Peri conceptional folic-acid supplementation can prevent most neural-tube defects and other congenital abnormalities of the cardiovascular system, urinary tract and limb deficiencies. Moreover, folic-acid supplementation in pregnancy is associated with the decreased incidence of habitual spontaneous abortion and pregnancy complications (e.g., placental abruption and preeclampsia)[26]. No drug pertaining to US FDA risk category X was prescribed.

CONCLUSION

Our study concluded that the incidence of hypertensive disorders in pregnancy was high. Early diagnosis and treatment through regular antenatal checkup is a key factor to prevent PIH and its complications. The incidence of combination therapy was high. Methyldopa was the commonest prescribed antihypertensive in monotherapy and combination, as it is safest during pregnancy.

Generally, any medication unless absolutely necessary, should not be taken during pregnancy, particularly during the first trimester. Additional drugs were prescribed only if required. Findings of our study showed that all eligible pregnant women were provided with anti hypertensives in a right dose. The data collected represents the prescribing pattern in a tertiary care hospital to provide optimum healthcare to improve the overall health of the mother and baby in the community.

The study was safe as no fetal harm was noticed throughout the study period. The pregnant women were called for routine check up in order to overcome prescribing error if any based on the presenting complaints or symptoms from them as if left untreated or un noticed may lead to fetal harm and neonatal death too, special care was taken by clinical pharmacists by providing patient counseling and involving in pharmacist interventions.

Strengths: A prescription based survey is considered to be one of the most effective methods to assess drug utilization of medication. Recommendations of FDA drugs on pregnancy help to improve prescribing patterns of the prescriber and ultimately the Clinical Standards.

Limitations: In our study it was noticed that all the drugs were prescribed by brand name and not by generic name which is not an encouraging finding as it promotes a specific brand and creates confusion and may lead to prescribing errors for the pharmacist, involved in dispensing. Moreover it is a regional study.

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Volume : 6 | Issue : 9 | September 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

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Disclosure of interests: The authors have no Conflicts of Interest to declare.

Contribution to authorship: This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

Details of ethics approval: The Ethics committee of Owaisi Hospital and Research Centre approved the study to be carried out in the Department of Obstetrics and Gynaecology and gave the IRB letter on January 22nd , 2014.

RESULTS:

Table 1 shows the demographic data of pregnant women attending antenatal OPD.

Demographic data	Results (number(%))
Age (in years)	38.54±4.28
Literacy status	
Illiterate	62(20.6)
Primary education	85(28.3)
Secondary education	73(24.3)
Graduate	47(15.6)
Post graduate	33(11)
Employment	
Unemployed	197(65.6)
Employed	103(34.3)
Gravida	
Primi	98(32.6)
Secondary	111(37.1)
Multi	91(30.3)
Trimesters	
First	78(26)
Second	132(44)
Third	90(30)
Hypertensive Disorders	
Gestational htn	70(23.3)
Pre Eclampsia	162(54)
Eclampsia	46(15.33)
Chronic Hypertension	22(7.33)

Table 2 shows subject characteristics of study population:

Characteristic	Mean(n=300)
Age(in years)	38.54
Weight at the time of admission	66.8
Systolic Blood Pressure (mmHg)	155.6
Diastolic Blood Pressure (mmHg)	100.3
Mean Arterial Pressure(mm Hg)	118.7
Gestational age at enrolment (in weeks)	30.4

Table 3 shows age in years and no. of patients involved in our study, (N=300)

Age	No.of patients				
	Gest htn	Pre eclampsia	eclampsia	Chr htn	Number (%)
16-20	4	27	6	0	37(12.3)
21-25	24	72	18	4	118(39.3)
26-30	23	25	11	3	62(20.6)
31-35	9	29	10	5	53(17.6)
36-40	6	6	1	6	19(6.3)
41-45	4	3	0	4	11(3.6)

Figure 1 shows age in years and no. of patients involved in our study.

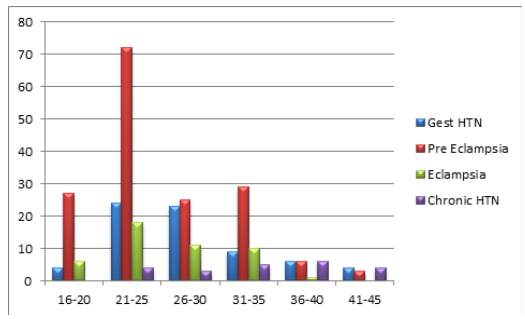

Table 4 shows gravida status and no. of patients involved in our study,(N=300)

Gravida	No.of Patients				
	Gest htn	Pre eclampsia	eclampsia	Chr htn	Number (%)
Primi	14	72	12	0	98(32.6)
Second	34	52	16	9	111(37.1)
Multi	22	38	18	13	91(30.3)

Figure 2 shows gravida status and no. of patients involved in our study,

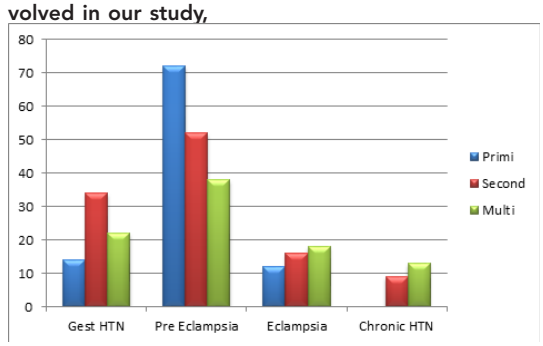

Table 5 shows Trimester of patients involved in the study: (N=300)

Trimester	No. of patients (%)
Trimester I (1-12weeks)	78 (26)
Trimester II (13-27weeks)	132 (44)
Trimester III(28-40weeks)	90 (30)

Figure 3 shows Trimester of patients involved in the study

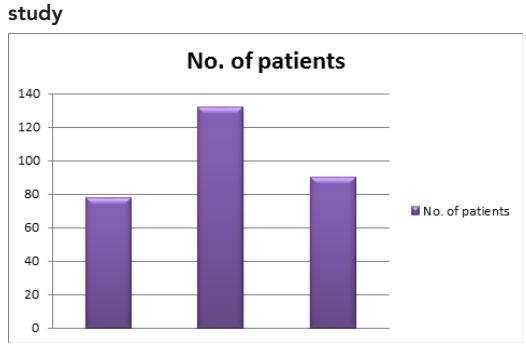

Table 6 shows Gestational Age of patients involved in our study. (N=300)

Gestational Age(in weeks)	Gestational HTN	Pre Eclampsia	Eclampsia	Chronic Hypertension	Number (%)
≤ 20	8	6	5	0	19(6.33)

Volume : 6 | Issue : 9 | September 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

21-24	10	21	7	4	42(14)
25-30	11	33	17	7	69(23)
31-35	19	63	11	6	101(33.6)
≥36	21	37	6	5	69(23)

Figure 4 shows Gestational Age of patients involved in our study.

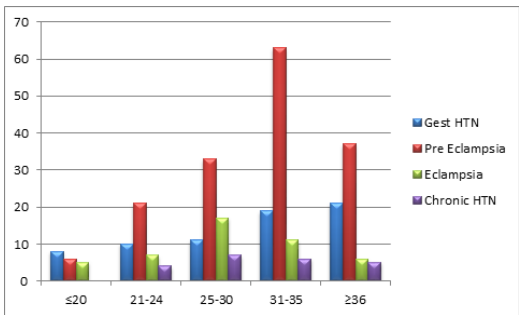

Table 7 shows symptoms of patients with hypertensive disorders of pregnancy.(N=128)

Symptoms	Patients (%)
Peripheral edema	43(33.5)
Severe headache	20(15.6)
Epigastric pain	25(19.5)
Blurred vision	12(9.37)
Seizures	28(21.8)

5 shows symptoms of patients with hypertensive disorders of pregnancy.

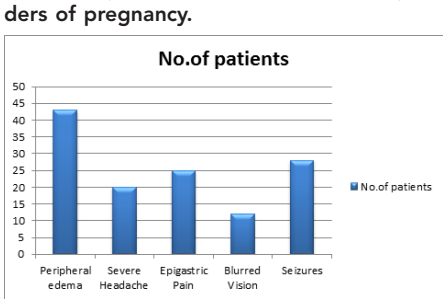

Table 8 shows prescribing pattern of Anti Hypertensives:

Prescribing pattern	Number (%)
Monotherapy	140(46.6)
Combination Therapy	160(53.3)

Figure 6 shows prescribing pattern of Anti Hypertensives

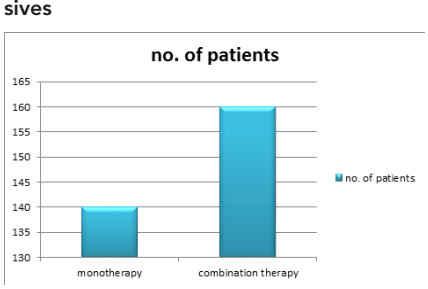

Table 9 shows Pattern of anti hypertensive drugs prescribed in patients treated with combination therapy (n= 160)

Drug class	Patients (%)
CAA+CCB	40(25)
CCB+ βBA	15(9.37)
CAA+βBA	17(10.62)
CAA+DIURETIC	18(30)
CCB+DIURETIC	26(16.25)
CAA+CCB+ βBA	13(8.12)
CCB+ βBA+CCA+DIURETIC	31(19.37)

Figure 7 shows Prescribing pattern of anti hypertensives in patients treated with combination therapy.

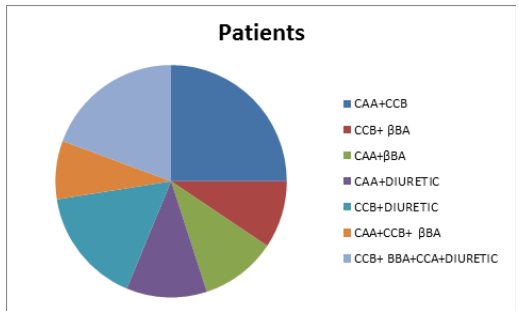

Table 10 shows prescribing pattern of various anti hypertensive drugs(monotherapy+ combination therapy) N=300.

Drugs prescribed	G. htn	Pre clampsia		Eclampsia	Chr htn	Number (%)
		mild	severe			
Nefidipine	8	10	12	3	0	33(11)
Methyldopa	16	14	11	0	0	41(13.6)
Nefidipine + methyldopa	8	37	41	5	5	96(32)
Methyldopa+labetalol	8	8	8	0	0	24(8)
Nefidipine+labetalol	0	16	8	3	0	27(9)
Atenolol+nefidipine	8	0	8	0	0	16(5)
Nefidipine+furosemide	8	0	0	0	0	8(2)
Methyldopa+ furosemide	0	0	0	3	0	3(1)
Labetalol+ nefidipine+ methyldopa	8	0	21	0	0	29(9)
Methyldopa+nefidipine +labetalol+atenolol	0	0	15	0	0	15(5)
Methyldopa+nefidipine +labetalol+furosemide	0	0	8	0	0	8(2)

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Volume : 6 | Issue : 9 | September 2016 | ISSN - 2249-555X | IF : 3.919 | IC Value : 74.50

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