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Study of Intradialytic Hypertension: A Single Centre Analysis

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ABSTRACT

In India around 20,000 people are dependent upon hemodialysis. The greatest burden of morbidity and mortality for hemodialysis patients are cardiovascular diseases (CVDs) including fluctuations in blood pressure, as CVDs account for approximately 50% of all deaths. Intradialytic hypertension (IDH) is one such complication responsible for increased morbidity and mortality in chronic kidney disease (CKD) patients undergoing hemodialysis. In India, there is limited data available in the literature for the incidence of IDH in CKD patients on hemodialysis. In this observational study, we evaluated the incidence of IDH in Indian CKD patients undergoing hemodialysis. We found a higher incidence of IDH (34.51%) in our cohort than in Western studies. These patients were further evaluated for the association of IDH with contributory factors and patient outcomes after one year of follow-up. This analysis yielded a novel finding of a higher incidence of IDH in patients with lower creatinine, which needs to be confirmed with multicenter trials.

KEY WORDS: Intradialytic hypertension; Chronic kidney disease (CKD); Hemodialysis.

ABBREVIATIONS: CVDs: Cardiovascular diseases; IDH: Intradialytic hypertension; CKD: Chronic Kidney Disease; ESA: Erythropoietin-stimulating agent;

INTRODUCTION

In India around 20,000 people are dependent upon hemodialysis.[1] The greatest burden of morbidity and mortality for hemodialysis patients are cardiovascular diseases (CVDs), which accounts for approximately 50% of all deaths.[2] Fluctuations in blood pressure (BP) is one of the most common complication that occurs in patients taking hemodialysis. A recent study from South Africa showed that intradialytic hypertension (IDH) may affect as many as 28% of the dialysis population.[3] The only Indian study, reported from south India in 2016, looked at the incidence of IDH on the Indian hemodialysis population but did not study the factors responsible for IDH and the impact of IDH on mortality.[4] The aim of this study was to evaluate the incidence of IDH, to study factors responsible for IDH and effect of IDH on mortality in patients attending regular dialysis sessions at a single dialysis unit.

MATERIALS AND METHODS

The present study was conducted on 142 patients with chronic kidney disease (CKD) undergoing maintenance hemodialysis at the dialysis centre of MGM Medical College & Hospital, Aurangabad, Maharashtra, India. This was a prospective observational cohort study over a period of 2.5 years from January 2013 to June 2015. All CKD patients over 18 years of age were included in the study. Patients of acute kidney injury were excluded. Primary end point was the development of IDH by patients undergoing regular hemodialysis. Secondary end points were potential biological markers associated with IDH and mortality in all patients. IDH was defined as an increase in systolic blood pressure of more than 10 mmHg during hemodialysis more than

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two hemodialysis sessions.[5] Using this definition, patients were stratified into IDH & Non-IDH categories for analysis.

Potential associated factors which were studied include age, sex, known case of hypertension (HTN) or diabetes mellitus, serum creatinine level, IV erythropoietin use, oedema, serum albumin level, and number of anti-hypertensive drugs. All patients were observed for one year to determine the mortality rate.

Dialysis prescription used for patients included in our study was as follows:

- Dialyser- Nipro elision 13 M synthetic polynephron
- Time- 4 hours
- Blood flow rate- 200-300 ml/hour
- Dialysate flow rate- 500 ml/hour
- Ultra filtration rate- as per weight gain
- Dialysate composition- Na^{++} 135-145 meq/L, K^{+} 0-4 meq/L, Ca^{++} 2.5-3.5 meq/L, Mg^{++} 0.5-0.75 meq/L, Cl 98-124 meq/L, Acetate 2-4meq/L, HCO_3 30-40 meq/L, Dextrose 11 g, pH 7.1-7.3
- Dialysate temperature- 36 ºC to 37 ºC
- Anticoagulation- Heparin 2000 IU at start of hemodialysis & 1000 IU per hour

Dialysis prescription was modified for IDH patients in the form of ultrafiltration rate and time of hemodialysis session. Patients who had IDH were treated either with injectable metoprolol 5 mg or injectable labetalol 20 mg with dose modified as per need. Effect of these drugs on IDH and on outcome was not studied in our study. The study was conducted in accordance with the ethical principles set out by the declaration of Helsinki and approval for the study was granted by the Human Research Ethics Committee of MGM University of Health Sciences (Registration Number- ECR/581/Inst/2013).

Statistical Analysis

SPSS software version 20 was used for the analysis of this data. Chi-square test was applied to check significant association between different groups and outcome of different attributes. *p*-value was checked at 5% level of significance.

RESULTS

Out of 142 patients, 49(34.51%) patients were found to have IDH (Figure 1). Among them 33(67.34%) were male, 30(61.22%) were above 60 years of age, 39(79.59%) were hypertensive, 10(20.41%) were diabetic, 34(69.38%) patients were receiving IV erythropoietin, 33(67.35%) were oedematous, 26(53.06%) had a serum albumin less than 2.5 mg/dL. 21(53.85%) patients

Graph 1: Incidence of IDH.

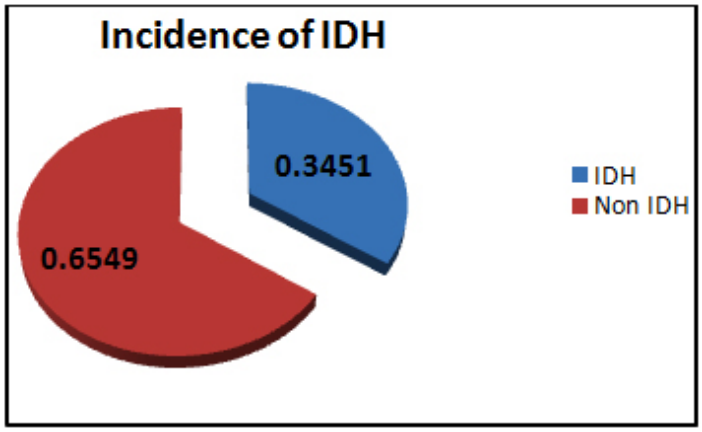

Table 1: Results Showing Non-modifiable Factors Responsible for IDH.

Factor		Results: IDH	Results: NON IDH	*p*-value
Age	>60 years	30 (61.22%)	60 (64.52%)	*p*=0.699
	<60 years	19 (38.78%)	33 (35.48%)	NS
Sex	Male	33 (67.34%)	70 (75.27%)	*p*=0.315 NS
	Female	16 (32.66%)	23 (24.73%)	

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Table 2: Results Showing Modifiable Factors Responsible for IDH.

Factor		Result		
		IDH	Non-IDH	*p*-value
Hypertension	HTN	39 (79.59%)	69 (74.19%)	*p*=0.474
	Non-HTN	10 (20.41%)	24 (25.81%)	NS
Diabetes mellitus	Diabetic	10 (20.41%)	16 (32.66%)	*p*=0.639
	Non-Diabetic	39 (79.59%)	77 (82.80%)	NS
Serum creatinine	<10 mg/dL	42 (85.71%)	61 (65.60%)	*p*=0.003
	>10mg/dL	7 (14.29%)	32 (34.40%)	S
Erythropoietin IV	EPO	34 (69.38%)	41 (44.09%)	*p*=0.004
	Non-EPO	15 (30.62%)	52 (55.91%)	S
Oedema	Oedematous	33 (67.35%)	30 (32.26%)	*p*<0.0001
	Non-Oedematous	16 (32.65%)	63 (67.74%)	S
Serum albumin	<2.5 mg/dL	26 (53.06%)	30 (32.26%)	*p*=0.016
	>2.5 mg/dL	23 (46.94%)	63 (67.74%)	S
No. of antihypertensive drugs	<2 drugs	21 (53.85%)	49 (71.01%)	*p*=0.073
	>2 drugs	18 (46.15%)	20 (28.99%)	NS

IDH Intradialytic hypertension; HTN Hypertension.

were taking less than two anti-hypertensive drugs. 19(38.77%) patients died within 1 year of study initiation. Novel finding was 42(85.71%) patients among IDH population had serum creatinine less 10 mg/dL A detailed description of all factors is listed in Tables 1 and 2.

DISCUSSION

The present study is a prospective observational study of the incidence of IDH in CKD patients undergoing maintenance hemodialysis. A total of 142 CKD patients were studied over a period of 2.5 years. Out of 142 patients, 49 were found to have IDH with incidence of 34.51%, which was greater than the incidence found in western studies by Stidley et al[6], Mees D[7], in which it was found to be 5-15%. A recent study from South Africa showed that IDH may affect as many as 28% of the dialysis population.[3] None of these studies focused in the Indian patient population. One study from South India by Darimireddi SK et al[4] found the incidence of IDH to be 49% in 100 patients studied. This supports our finding that the incidence of IDH is higher in Indian population.

Out of 142 patients in our study, 103 were males and 39 were females. 90 patients were above 60 years of age. In this study, no relation was found between the incidence of IDH and the age or sex of the patient. No previous studies demonstrated a statistically significant difference among males and females. According to a study by Inrig et al[5] on 32,295 patients, incidence of IDH was found more amongst the elderly. Similarly, in our study we found that IDH occurred more frequently in the elderly but it was not statistically significant.

No significant relationship was found between the incidence of IDH and previous HTN or diabetes in CKD patients. Although, no study examined the burden of IDH in known hypertensive patients, removal of anti-hypertensive medications during hemodialysis is one of the proposed mechanisms for IDH.[8] No comparable data regarding the relationship of diabetes mellitus and IDH was found in previous studies.

A significant inverse relationship was found between the incidence of IDH and serum creatinine level, with a higher incidence of IDH in patients with lower serum creatinine levels (Figure 2). In a study previously published by Inrig et al[9] patients who experienced IDH were thinner, had lower muscle mass (lower serum creatinine) and were more likely to experience a rise in blood pressure (BP) with minimal volume excess. Similarly, in our study occurrence of IDH among patients with lower creatinine value was statistically significant with greater incidence of IDH in lower creatinine group. Majority of our study population were frail, mostly due to malnutrition and the disease itself. Acute intradialytic changes in endothelial cell function have been proposed as etiologies for the increase in vascular resistance, although it is unclear if endothelin-1 or some other vasoconstrictive peptide is responsible. Chou et al[10] demonstrated imbalances in endothelial cell-derived mediators after dialysis in the IDH patients. Specifically, there were higher levels of the vasoconstrictor endothelin-1 (ET-1) and smaller ratios of the vasodilator nitric oxide to ET-1. Karakelleoglu et al[11] showed that the patients with malnutrition have higher endothelin-1 levels. Recent study by Park et al[12] indicate that lower creatinine levels in patients undergoing hemodialysis are associated with lower muscle mass, malnutrition, and mortality. These findings sup-

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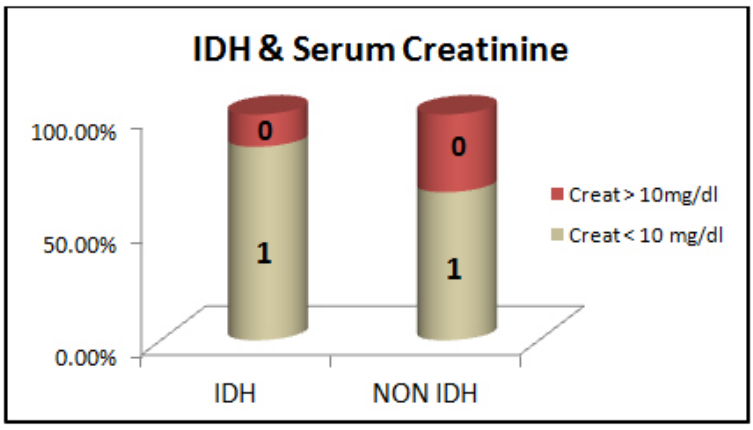
Graph 2: IDH and Serum Creatinine Co-Relation.



port that lower creatinine level which is a marker for malnutrition and is responsible for IDH through ET-1 mediated IDH.

A study by Sarkar SR et al[13] found an increased incidence of IDH among patients receiving IV erythropoietin therapy. A study by Abraham et al[14] found that 21% of patients had clinically important increases in BP during treatment of anaemia with erythropoietin. In a small investigation of the acute effects of erythropoietin-stimulating agent (ESA) in hemodialysis patients within 30 minutes following intravenous ESAs, there was a significant increase in ET-1 and a concomitant rise in mean arterial pressure (MAP) which was not demonstrated in patients given subcutaneous ESA or placebo.[12] In addition, 53% (10/19) of patients given intravenous ESA, had an increase in MAP>10 mmHg in the intradialytic period. Thus, if ESA is given intravenously, prior to the end of hemodialysis, it is possible that this may contribute to development of IDH in susceptible patients. It is possible that vasoconstriction, arising due to improved tissue oxygenation may result in IDH in some patients. In our study, incidence of IDH was higher in patients receiving IV erythropoietin during hemodialysis sessions, which was found to be statistically significant. This result was similar to studies done by Abraham et al[14] and Buckner et al.[15]

A significant relationship was also found between incidence of IDH and presence of oedema, with greater incidence of IDH in oedematous patients secondary to volume overload. Similar findings were shown in studies by Inrig et al[9] and Agarwal et al.[16] It was also observed that BP may paradoxically rise with ultrafiltration, when patients are volume overloaded. In a study by Inrig et al[9] it was found that incidence of IDH was higher in patients having low serum albumin levels. Similar results were found in our study. The mechanism of IDH may be due to reduced blood viscosity causing high cardiac output and increased peripheral vascular resistance.

In the Inrig et al[9] study, it was found that IDH incidence was greater in hypertensive patients who were prescribed greater number of anti-hypertensive drugs compared to those who were given standard regimen. In our study, incidence of IDH was more with patients receiving more than two anti-hypertensive drugs than patients receiving less than two anti-hypertensive drugs but it was statistically not significant. It is studied in literature that there is an association between dialysate to serum sodium gradients and BP increase during dialysis in patients with IDH, although it is unclear if this is related to endothelial cell activity or acute osmolar changes. In addition to probing the dry weight of patients with intradialytic hypertension, other management strategies include lowering dialysate sodium and changing anti-hypertensives to include carvedilol or other poorly dialyzed anti-hypertensives will help to reduce IDH.[17] All patients in our study were prescribed similar dialysis prescription to remove this confounding factor, and all patients of IDH were prescribed non-dialyzable anti-hypertensives for treatment of IDH. Except angiotensin receptor blocker (ARB) and angiotensin-converting enzyme (ACE) inhibitors, most of other drugs are dialyzed and hence incidence of IDH is more when more drugs are prescribed.

A significant relationship was found between incidence of IDH and survival of CKD patients. Patients having IDH had a more frequent occurrence of deaths at one year (Figure 3). Inrig et al[18] in a cohort of 438 prevalent hemodialysis patients, demonstrated that systolic BP elevations of more than 10 mmHg with hemodialysis are associated with a 20% increased odds of death or hospitalization at 6 months. Inrig et al[9] also demonstrated that increasing systolic BP in incident hemodialysis patients was associated with poorer 2-year survival.

CONCLUSION

Incidence of IDH in our study was 34.51% which was higher than what was found in the African study.[3] Only one Indian study showed incidence of 49% in 100 patients studied.[4] This suggests incidence of IDH is more in Indian population. Prognosis of CKD patients was worse among IDH group as 38.77% patients died within 1 year. We found a statistically significant relation between incidence of IDH and serum creatinine level, use of IV erythropoietin, oedema, and serum albumin level. However, no

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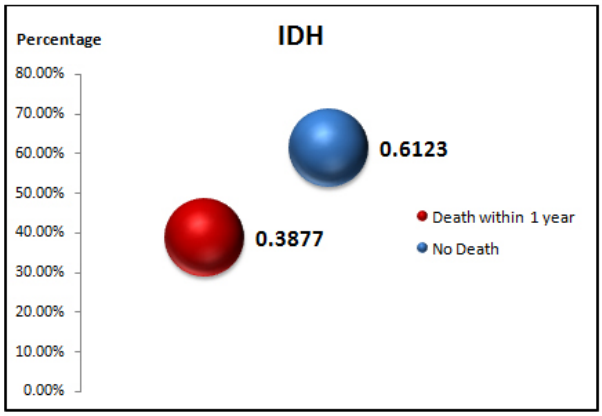
Graph 3: Results Showing Death within 1 Year of IDH.



significant relation was found between incidence of IDH and age of the patient, sex of the patient, hypertension, diabetes mellitus and number of anti-hypertensive drugs.

IDH is preventable if we control modifiable risk factors such as avoiding use of IV erythropoietin, reducing interdialytic weight gain, correction of serum albumin. This will reduce cardiovascular morbidity and mortality in CKD patients on maintenance hemodialysis. This is the first study in India which showed factors responsible for IDH and impact of IDH on mortality in Indian population. The other Indian study[4] has studied only incidence of IDH without studying factors responsible for IDH and its impact on mortality. No studies in literature till date evaluated the role of previous hypertension or diabetes with incidence of IDH. There was no association found between IDH and hypertensive or diabetic status of patient in our study. Higher incidence of IDH in patients with lower creatinine is a novel finding which needs to be confirmed with multicenter trials. Thus, IDH is an important cardiovascular event in Indian hemodialysis population which contributes to increased mortality in patients on hemodialysis although its exact pathogenesis is not known. Measures should be taken to reduce its incidence in hemodialysis patients.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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