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# A Study To Evaluate The Efficacy Of Tolvaptan In Correction Of Hyponatremia And Its Effect On Urine Output In Relation With Serum Albumin Level In Patients Of Alcoholic Chronic Liver Disease.

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***Abstract:*** *Chronic liver disease is a phenomenon associated with volume overload and its main stay treatment is loop diuretics. The dose is usually increased until diuresis is satisfactory. However if the diuresis remains unsatisfactory few alternative therapeutic options are available[1]. Tolvaptan , a novel diuretic agent that acts on distal nephron to allow excretion of electrolyte free water ( aquaresis ), thereby exerting its pharmacological action without causing electrolyte imbalance. Tolvaptan also known as OPC-41061, is an orally acting nonpeptide, AVP antagonist[2]. It is observed that tolvaptan leads to greater 24 hour urine volume/excretion rate than furosemide and hydrochlorthiazide. It is metabolised by CYP3A4 system and concomitant use of strong CYP3A4 inhibitors is to be used with caution.So, via this study an attempt is being made to assess the efficacy of tolvaptan in refractory ascites, keeping in view the change in serum albumin level from baseline and 24/hour urine output from baseline and correction of moderate hyponatremia in appropriate dose of the drug[5]. The study was an example of prospective cohort study with a study sample of 60 patients, 30 cases and 30 control. Duration of study was between April 2016 to October 2017 at , Dept of Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand,India.*

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## I. Introduction

Chronic liver disease is a phenomenon associated with volume overload and its main stay treatment is loop diuretics. The dose is usually increased until diuresis is satisfactory. However if the diuresis remains unsatisfactory few alternative therapeutic options are available. It is well known that increase in loop diuretic dose can lead to adverse events including renal impairment and electrolyte imbalance. Hypoalbuminemia is considered a reason for insufficient reponse to loop diuretics. Few therapeutic alternatives are available for patient with hypoalbuminemia.

An alternative said to be tolvaptan , a novel diuretic agent that acts on distal nephron to allow excretion of electroloyte free water ( aquaresis ), thereby exerting its pharmacological action without causing electrolyte imbalance. It is observed that tolvaptan leads to greater 24 hour urine volume/excretion rate than furosemide and hydrochlorthiazide. So, via this study an attempt is being made to assess the efficacy of tolvaptan in refractory ascites, keeping in view the change in serum albumin level from baseline and 24/hour urine output from baseline and correction of moderate hyponatremia in appropriate dose of the drug.

## II. Materials And Method

The study ia an example of prospective cohort study conducted over 60 patients, 30 cases and 30 control over a duration of april 2016 to October 2017.
Place of study: Dept of Medicine, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand,India.
Study design: prospective cohort study
Study duration: april 2016 to October 2017
Sample size: 60, 30 cases and 30 control

**INCLUSION CRITERIA:**
All patients of alcoholic chronic liver disease diagnosed with history, clinical examination and investigation (some of them may require higher specialized investigations)

**EXCLUSION CRITERIA:**
All patients of alcoholic chronic liver disease who will be suffering from co-morbidities which may be a cause of hypoalbuminemia and can affect the efficacy of tolvaptan should be exclude, example diabetes mellitus, hypertension, chronic kidney disease etc.

## III. Methodology

Principle of methodology is to work on the basis of prospective study where a sample of 30 patients as control and 30 patients as study group will be taken and all patients will receive a combination of diuretics (40-80 mg/day of furosemide and 80-160 mg/day of spironolactone) Further tolvaptan ( 15 mg/day ) will be given for 5-14 days to the study group and the level of serum sodium, serum albumin and baseline urine output of both the groups will be measured and a comparison will be drawn at the end of study. The data collected during the study will be generated and caliberated in MS-EXCEL sheet, and statistical significance and p-value will be drawn using the excel sheet.

- Statistical Analysis

Sample size: 60 cases admitted in Rajendra Institute Of Medical Sciences,who met the inclusion and exclusion criteria, were informed about the process and informed consent was taken.
Data analysis: The SPSS software was used for data analysis( version 20.0). MS excel sheet was generated and foray of statistical data was done via graphs and piecharts respectively.
Satistical methods:
The tabulation of data collected was done unde two headings for case and control groups respectively. On the case group tolvaptan was added as a conventional drug and in the control group standard conventional therapy for Chronic liver disease with hyponatremia was given for a standard duration of 7-10 days. Depening on the data collected, three important variables were extrapolated namely, urine output, serum sodium and serum albumin before ansd after therapy for both case and control groups. The extrapolated data was analysed using paired t- test and chi square test with generation of p-value. And based on the p-value it was further exemplified that whether the study is significant or not. An alternate hypothesis was also generated incase p value<0.05 stating that the use of tolvaptan is not beneficial in the study.

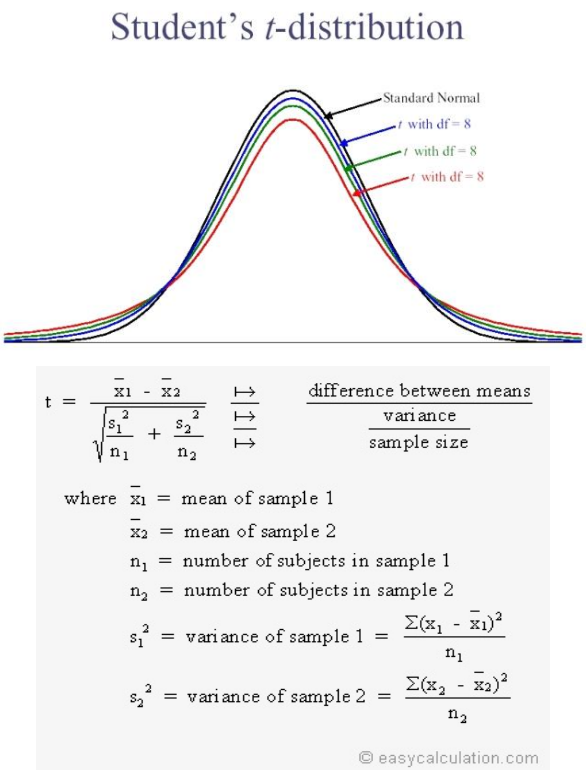


**Fig 1.** Shows student's t-test with Gaussian curve and formulation of t- test with variance analysis

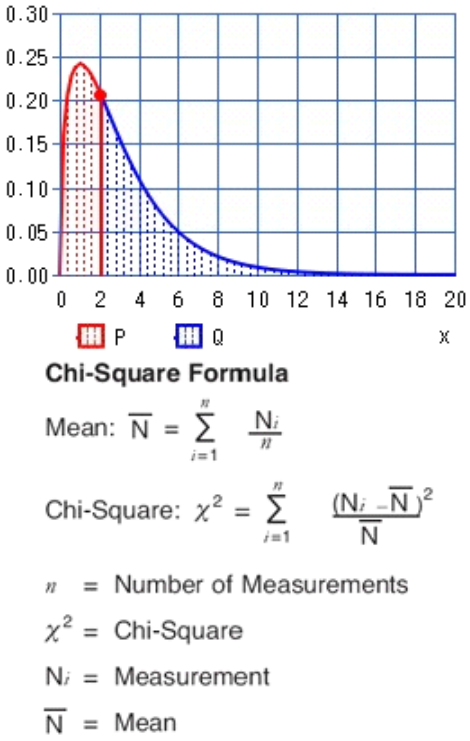


**Fig2.** Shows chi square test with calculation of p value for testing the efficacy of this study.

## IV. Results:

| Distribution of hepatic encephalopathy | Percentage Distribution |
|---|---|
| H.E. Present | 42% |
| H.E. absent | 58% |

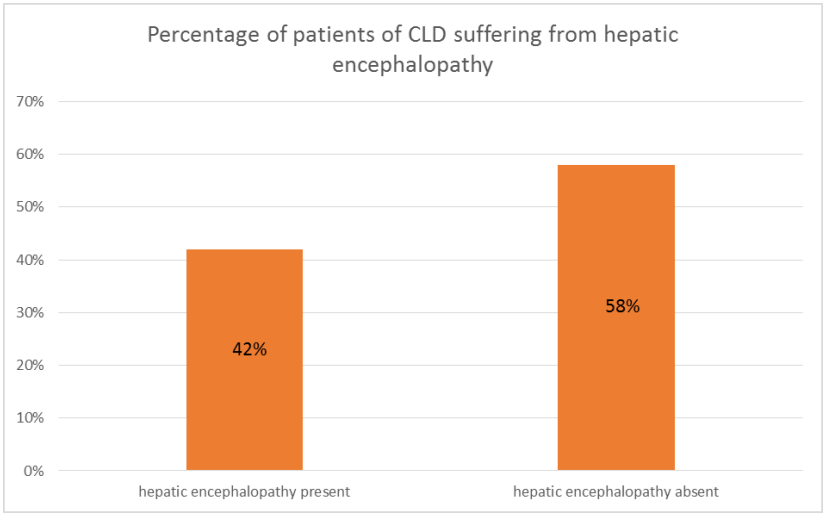


Table no 1. Percentage distribution of CLD suffering from hepatic encephalopathy 58% had no hepatic encephalopathy and 48% had hepatic enceohalopathy.

| Hepatic encephalopathy patients in case group | Recovered patients | Dead patients |
|---|---|---|
| 14 (56%) | 10 | 4 |
| Hepatic encephalopathy patients in control group | Recovered patients | Dead patients |
| 11 (44%) | 7 | 4 |

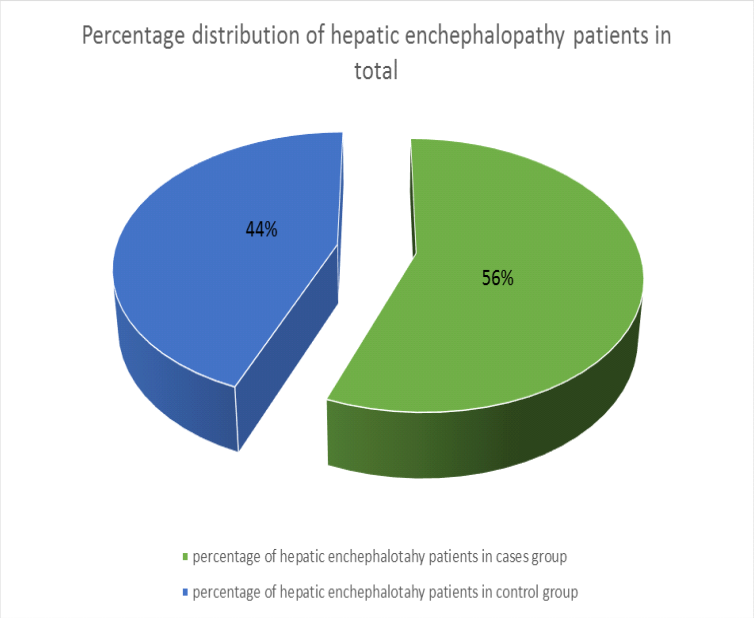


**Table no 2.** Percentage distribution of hepatic encephalopathy patients . 44% in control and 56% in case group.

| Status of hepatic encephalopathy in case group | Percentage distribution |
|---|---|
| Recovered | 71% |
| Dead | 29% |
| Status of hepatic encephalopathy in control group | Percentage distribution |
| Recovered | 63% |
| Dead | 37% |

**Table no 3**. showing distribution of recovery among hepatic encephalopathy patients. 71% recovered in case group and 63 in control group.

| Distribution of hepato-renal syndrome | Percentage Distribution |
|---|---|
| Present | 5% |
| Absent | 95% |

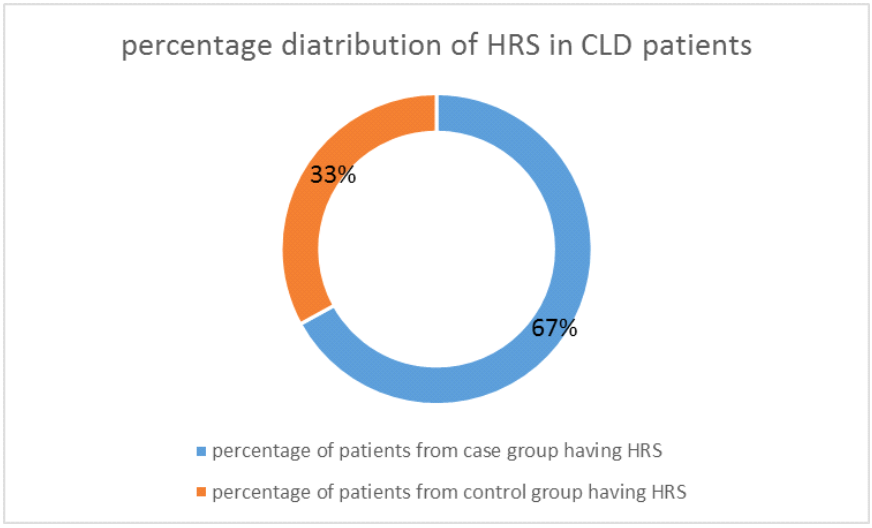


**Table no 4.** Percentage distribution of HRS(hepatorenal syndrome) in patients of CLD.67 had HRS in case group and 33% in control group.

**Table no 5.** comparison of values of serum albumin ,urine output and serum sodium level in case group before tolvaptan after tolvaptan.

| PARAMETER | BEFORE TOLVAPTAN (MEAN $^{+}$_S.D.) | AFTER TOLVAPTAN (MEAN +_ S.D.) |
|---|---|---|
| • SERUM ALBUMIN (mg/dl) | 3.04 +_ 0.22 | 3.2 +_ 0.227 |
| • URINE OUTPUT (ml) | 956.67 +_ 104 | 1300 +_ 0.11 |
| • SERUM SODIUM (meq/l) | 127 +_ 2.05 | 133 +_ 2.43 |

Shows comparison of values of serum albumin(mg/dl) ,urine output in(ml) and serum sodium(meq/lit) level in case group before tolvaptan and after tolvaptan therapy. This showed significant increase in values (MEAN+_S.D) after tolvaptan therapy in case group.

**Table no 6.** comparison of values of serum albumin, urine output and serum sodium level in control group before and after conventional therapy .

| PARAMETER | BEFORE CONVENTIONAL THERAPY (MEAN +_ S.D.) | AFTER CONVENTIONAL THERAPY (MEAN +_ S.D.) |
|---|---|---|
| • SERUM ALBUMIN (mg/dl) | 2.98 +_ 0.141 | 3.12 +_0.177 |
| 2. URINE OUTPUT (ml) | 1006.7 +_ 103 | 1180 +_ 0.115 |
| 3. SERUM SODIUM (meq/l) | 127 +_ 1.6 | 131 +_ 1.67 |

shows comparison of values of serum albumin(mg/dl) ,urine output in(ml) and serum sodium(meq/lit) level in control group before conventional and after conventional therapy. This showed increase in values (MEAN+_S.D) after conventional therapy but less than case group.

**Table no 8.** showing P-value after applying paired –t test for serum albumin, urine output, and serum sodium level in case and control group.

| PARAMETER | p- value |
|---|---|
| 1. SERUM ALBUMIN | 0.000927 |
| 2. URINE OUTPUT | 0.00178 |
| 3. SERUM SODIUM | 0.0007 |

| PARAMETER | p- value |
|---|---|
| • SERUM ALBUMIN | 1.809 |
| • URINE OUTPUT | 0.008 |
| • SERUM SODIUM | 0.008 |

Shows P- values of case and control group in which p- value of case group is significant and suggest significant improvement in urine output and serum sodium level after tolvaptan therapy and justify the use of tolvaptan in patients of CLD with hyponatremia with decrease urine output irrespective of serum albumin level. Whereas p- value of control group is not significant.

## V. Discussion

Chronic liver disease is a phenomenon associated with volume overload and its main stay treatment is loop diuretics. The dose is usually increased until diuresis is satisfactory[1]. However if the diuresis remains unsatisfactory few alternative therapeutic options are available. It is well known that increase in loop diuretic dose can lead to adverse events including renal impairment and electrolyte imbalance. Hypoalbuminemia frequently complicates liver cirrhosis[2]. The serum albumin level contributes to prevention of edema by balancing the hydrostatic and colloid osmotic pressure within blood vessel. The binding of drugs to serum albumin plays an important role in pharmacokinetics, drug distribution, drug metabolism. Hypoalbuminemia is considered a reason for insufficient response to loop diuretics. Few therapeutic alternatives are available for patient with hypoalbuminemia[3.]

An alternative said to be tolvaptan, a novel diuretic agent that acts on distal nephron to allow excretion of electrolyte free water (aquaresis), thereby exerting its pharmacological action without causing electrolyte imbalance. Tolvaptan also known as OPC-41061 is an orally acting nonpeptide, AVP antagonist[4].

So, via this study an attempt is being made to assess the efficacy of tolvaptan in refractory ascites, keeping in view the change in serum albumin level from baseline and 24/hour urine output from baseline and correction of moderate hyponatremia in appropriate dose of the drug.

## VI. Conclusion

Since the approval of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremiain 2009 , new studies have been reported to better characterize itz pharmacokinetis and pharmacodynamics profile of tolvaptan. This study is a review of previous clinical studies, and literarure, in order to guide appropriate clinical use of tolvaptan in patients alcoholic CLD.

In this study an attempt is being made to alleviate the fear of using tolvaptan in patients of alcoholic CLD for hyponatremia correction and increasing 24hr urinary output and irrespective of serum albumin level. Which is being made succesful to the extent where results are encouraging in favour of previous studies.

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