The Thesis Committee for Sahil Mittal Certifies that this is the approved version of the following Thesis:

METOLAZONE IN DIURETIC REFRACTORY ASCITES

Committee:

_____
Robert Beach, M.D., Supervisor

_____
Don W. Powell, M.D., Member

_____
Karl E. Anderson, M.D., Member

_____

Dean, Graduate School

METOLAZONE IN DIURETIC REFRACTORY ASCITES

by

Sahil Mittal, M.D.

Thesis

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Masters of Science in Clinical Investigation

The University of Texas Medical Branch

December 2011

Dedication

To my wife, Kamna Bansal for her unconditional love, wisdom, prayers and encouragement to follow my dreams

Acknowledgements

This thesis would not have been possible without the kind and generous support and guidance of my mentor, Dr Robert Beach. I would also like to thank Drs. Don Powell and Karl Anderson for their guidance and contribution. I would also like to express deep gratitude to Marie Carr and rest of the staff at Clinical Research Center for their assistance at every step of the way. Finally, I would like to express my gratitude to the Gastroenterology Division at the University of Texas Medical Branch and the Herzog foundation for providing the means to pursue this Masters of Science degree.

Metolazone in Diuretic Refractory Ascites

Publication No. _____

Sahil Mittal, MD

The University of Texas Graduate School of Biomedical Sciences,

At Galveston, Texas, 2011

Supervisor: Dr Robert Beach

Background: Refractory ascites occurs in about 10% of patients with cirrhosis and ascites. Available treatment options are invasive and costly procedures with significant complication rates. We hypothesized that adding metolazone; thiazide like diuretic, to conventional diuretics in these diuretic refractory patients may convert them to a diuretic sensitive stage and promote natriuresis. We conducted a pilot study to examine the efficacy of metolazone in diuretic refractory ascites.

Methods: Patients with refractory ascites were randomized to two groups. Group 1 received 10 mg of metolazone and Group 2 received 80 mg of furosemide. Both groups received their basal diuretic regimen. 24 hour urinary sodium was measured to compare the two groups.

Results: Metolazone group increased their 24 hr sodium excretion by 127±150.4 meq as compared to 44.5± 32.6 meq in the furosemide group (p=0.1). Average increase in urine output in the metolazone group was 1513ml as compared to 457ml for furosemide group.

Conclusion: Metolazone increased natriuresis by almost 3 times as compared to furosemide. Although the results were statistically not significant due to small sample size, these pilot observations indicate that further studies are needed to investigate role of metolazone in diuretic refractory ascites.

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List of Abbreviations

1. LVP – Large volume paracentesis
2. TIPS - Transjugular intrahepatic portosystemic shunt
3. AASLD - American Association for the Study of Liver Diseases
4. PCT - Proximal tubular cells
5. ECF – Extracellular fluid
6. GFR - Glomerular filtration rate
7. HCV – Hepatitis C

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CHAPTER 1

INTRODUCTION

Ascites is a common manifestation of cirrhosis of the liver and marks in many cases the transition from compensated to decompensate cirrhosis. In 10–20% of cirrhotic patients, ascites becomes refractory to diuretics and sodium restriction (1). The treatment options for these patients are:

1. **Liver transplantation**: The main hindering factors are organ shortage, cost and morbidity of the procedure and also the complications of immunosuppression.

2. **Large volume Paracentesis (LVP)**: Serial LVP leads to greater protein and complement depletion compared to diuretic therapy, which may predispose to ascitic fluid infection and further clinical deterioration (2, 3). Circulatory derangements after paracentesis are marked by renal impairment and decreased survival. Plasma expansion with albumin infusion (6–8 g/L of ascites removed) is recommended to prevent this circulatory dysfunction but the extremely high cost of albumin and repeated hospital visits makes this option cost ineffective (4).

3 **Transjugular intrahepatic portosystemic shunt (TIPS)**: Hepatic encephalopathy occurs in approximately 30% of patients after TIPS and significantly impairs quality of life. Because shunt stenosis rate is high (70% in 1 year), shunt revision is often needed. Cost is another hindrance. The procedure related complication rate is around 9% (5).

The practice guidelines on management of ascites published by the American Association for the Study of Liver disease (AASLD) mentions the above listed treatment options for diuretic refractory ascites (6). Understandably, complication rates, cost and patient acceptability limit treatment choices. Understanding the pathophysiological changes that progress in cirrhotics and in developing resistance to the conventional diuretics (furosemide and spironolactone) can help in finding better drug combination for control of ascites.

In the earliest stages of ascites, urinary sodium excretion is plentiful and negative salt balance can be achieved by simply lowering dietary sodium intake. As the disease advances, neurohumoral effects are activated resulting in more intense renal salt retention. Eventually, the filtered load of sodium is completely reabsorbed by the renal tubules and urine becomes virtually devoid of salt. At this stage, adding spironolactone will promote natriuresis by inhibiting reabsorption of the filtered sodium load that reaches the collecting duct or beyond. Once the disease progresses further, much of the filtered salt load is reabsorbed proximal to the collecting duct and at this stage thiazides and loop diuretics can be added to spironolactone to increase urinary sodium excretion. Eventually, the majority of the filtered load is reabsorbed proximal to the thick ascending limb of Henle. This effect can be explained by activation of neurohumoral factors that increases sodium reabsorption by the proximal tubular cells. At this point the patient is resistant to conventional diuretics (furosemide and spironolactone) and requires more invasive procedures such as LVP to remain in salt balance (7, 8).

The enhanced sodium reabsorption by the PCT has been shown to be secondary to angiotensin II and norepinephrine that stimulate (Na/K)-ATPase and apical Na-H exchanger. These endogenous anti-natriuretic substances: angiotensin II and norepinephrine are overproduced in cirrhosis (9). Although most diuretics stimulate renin secretion by reducing the ECF volume, only loop diuretics stimulate renin secretion at the macula densa. Thus, when ECF volume contraction is prevented, diuretics such as metolazone, a thiazide-like diuretic, have little effect on renin secretion. In contrast, even under these conditions, loop diuretics stimulate renin secretion (10). When loop diuretics are given for a prolonged period, renal rennin gene expression is strongly upregulated in a volume –independent manner (11).To minimize the occurrence of these adaptive changes that limit diuretic effectiveness, we suggest that metolazone should be added to low dose loop diuretics.

The afferent vasoconstriction is one of the pathogenic mechanisms in development of refractory ascites (12). This leads to efferent arteriolar constriction to increase the intra-glomerular pressure to maintain glomerular filtration. The net effect is to increase the filtration fraction in the glomerulus, and the concentration of plasma proteins in the glomerular capillaries increases and oncotic pressure rises. This step up in oncotic pressure is transmitted to the first branches of peritubular capillaries at the

level of proximal tubule and favors more sodium reabsorption by passive Starling forces, thus further increasing fluid absorption at the proximal tubules.

As outlined above, the pathophysiological changes that lead to increased proximal tubular sodium absorption explain progression to a diuretic resistant stage, simply because the conventional diuretics used in ascites (furosemide and spironolactone) are more effective at distal nephron segments where sodium delivery is markedly decreased. Acetazolamide, a carbonic anhydrase inhibitor, acts at the proximal tubule but has a high incidence of acid/base disturbances and cannot be used for a long period because of tachyphylaxsis. On the other hand, metolazone is a thiazide like diuretic that decreases sodium and chloride reabsorption at proximal and distal convoluted tubule and is a good candidate for decreasing proximal tubular reabsorption of sodium. Metolazone has been used extensively in the management of edema states (13). Examples include use in diuretic refractory nephrotic syndrome and severe congestive heart failure (14-16). In most of these studies the dose of metolazone was 10 mg/day (13).We hypothize that metolazone added to low dose furosemide will lead to greater natriuresis as compared to increasing the furosemide to a high dose. In a single dose equivalence study, Lowenthal and co-workers compared 10 mg metolazone with 80 mg of furosemide (17). An increase of furosemide by 80 mg is sufficient to determine if a patient will have any significant increase in natriuresis with this drug.

The ultimate goal is to improve medical therapy for diuretic refractory ascites and convert these patients to a diuretic sensitive state, which may prevent or delay the use of more invasive procedures in these patients. The pilot project has provided information on the degree of natriuresis with metolazone and the variability of response in patients with refractory ascites. These preliminary results will help in the design of larger randomized trials.

Chapter 2

Methods

The pilot study was approval by the Institutional Review Board of at UTMB, Galveston.

2.1 Methodology

Inclusion criteria

1. Patients admitted to the University of Texas Medical Branch (UTMB) hospital or Texas Department of Criminal Justice Hospital in Galveston for therapeutic paracentesis for control of ascites.
2. Age between 30 -75 years
3. Cirrhosis is confirmed either with biopsy or based on history, physical examination and laboratory and other investigations (imaging, endoscopy)
4. Being maintained on fixed doses of furosemide and spironolactone for at least 10 days before starting the study.

Exclusion criteria

1. Renal insufficiency with glomerular filtration rate (GFR) less than 30 ml/minute as measured by the MDRD formula: GFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
2. Severe hyponatremia with serum sodium < 120 meq/L
3. Hypokalemia with serum potassium < 2.5
4. Allergy to thiazide diuretics or metolazone or sulphonamides
5. Presence of flapping tremors (suggestive of hepatic encephalopathy)
6. Positive pregnancy test
7. Presence of hepatocellular carcinoma (confirmed either by imaging or by pathology).
8. Presence of tense ascites requiring immediate paracentesis
9. Spontaneous bacterial peritonitis

Criteria for removing patients from the study

1. Development of severe hyponatremia or hypokalemia during the study (defined as: Na level is <120, K level <2.5)
2. Worsening renal insufficiency with fall in GFR by more than 25% of the admission GFR or with an increase in serum creatinine of more than 0.5 mg/dl above the admission creatinine (creatinine will be measured and GFR will be calculated by using MDRD formula as outlined above).

3. Paracentesis any time during the study

Patients that were hospitalized for control of ascites and meet inclusion criteria were approached and the study and its risks and benefits explained in detail. All patients were offered paracentesis as an alternate to study enrollment and assured that not enrolling would not affect their care at UTMB.

The patients were assigned to one of two groups with block randomization. During the initial 12 hours of admission, patients continued their current doses of furosemide and spironolactone. Meanwhile baseline sodium excretion and GFR (using the MDRD formula and serum electrolytes) were measured.

Group 1: in addition to their home dose of spironolactone and furosemide, 10 mg of metolazone was added to the regimen.
Group 2: in addition to their current doses of lasix and spironolactone, 80 mg of furosemide was added to the regimen.
The patients in both groups were maintained on this regimen for 24 hours and meanwhile their urine output and 24-hour sodium excretion were measured.
The change in sodium excretion after adding metolazone or increasing the dose of furosemide was compared.

2.2 Data and safety monitoring plan

Throughout the hospital stay the patients were monitored hemodynamically (vital signs every 8 hours). Blood was drawn every 8 hours by means of venipuncture to measure the metabolic panel. Any disturbances in the serum electrolytes were corrected accordingly to standard medical practice.

Any adverse events (expected or unexpected) were recorded. Subjects were provided with contact information for the principal and co-investigator, if they have any questions, concerns or complaints before, during or after the study.

Data were recorded on electronic files saved on the computer used by the principal investigator. All identifiers were removed prior to data analysis.

2.3 Statistical Analysis

Sample Size Justification: We conducted sample size estimation for the main outcome variable of urine sodium. We used data from a report by Arnold (18). This study resembles our study design and compared furosemide with furosemide plus metolazone combination. They reported mean ±SD of 33±49 meq/day in the furosemide group and 169±168 meq/day in the furosemide plus metolazone group. We considered a difference of 70 to be a clinically significant difference in improvement.

We used a standard deviation of 50 for these calculations. A sample size of 10 in each group will have 84% power to detect a difference in means of 70 using a two-group t-test with a 0.05 two-sided significance level

Statistical Analysis: We conducted mostly descriptive analyses and created summary tables and plots of the data. This included measures of variation. Continuous data were compared with Wilcoxon exact test instead of T –test because of small sample size and categorical data compared with chi-square tests. Multivariate analysis was done to adjust for confounding factors.

Chapter 3

Results

34 subjects were approached. Out of 9 subjects that met inclusion criteria, 2 declined and rest 7 subjects were enrolled. 1 subject dropped out after enrollment. Their demographics are shown in Table 1. Three subjects were randomized to Group 1 i.e. received 10 mg of metolazone and four subjects were randomized to Group 2 and received 80 mg of furosemide. Both groups received their baseline regimen of diuretics. All were males except for subject 1. 3 each were Caucasian and Hispanic while 1 subject was of African American descent. Hepatitis C was the cause of liver disease in all the study subjects. The mean age in the two groups was comparable (55 ± 4.6 vs. 55± 7.9, p=0.6). MELD score in Group 1 was lower then Group 2 (p=0.09, Table 1). For Group 1 the median dose of baseline furosemide dose was 80 mg (mean 107 ± 8.0 mg) as compared to median dose of 60 mg (mean 55 ± 30 mg) in Group 2 (p=0.29). For spironolactone the baseline dose regimen was (Group 1 – median 200mg, mean 200mg, Group 2- median 75 mg, mean 100 mg, p=0.14).

	Age	Sex	Race	Etiology	MELD	Furosemide	Spironolactone
Group 1	Years					mg/day	mg/day
1	60	F	Black	HCV	11	80	200
2	54	M	White	HCV	13	80	200
3	51	M	White	HCV	7	160	200
Mean±SD	55±4.6				10.3±3.1	106.7±7.9	200±0
Median	54				11	80	200
Group 2							
4	43	M	Hispanic	HCV	18	40	100
5	52	M	Hispanic	HCV	20	80	200
6	64	M	White	HCV	13	20	50
7	49	M	Hispanic	HCV	16	80	50
Mean±SD	52±8.8				16.8±2.9	55±30	100±70.7
Median	50				17	60	75

Table1: Demographics and clinical features of patients. Group 1- Metolazone & Group 2- Furosemide

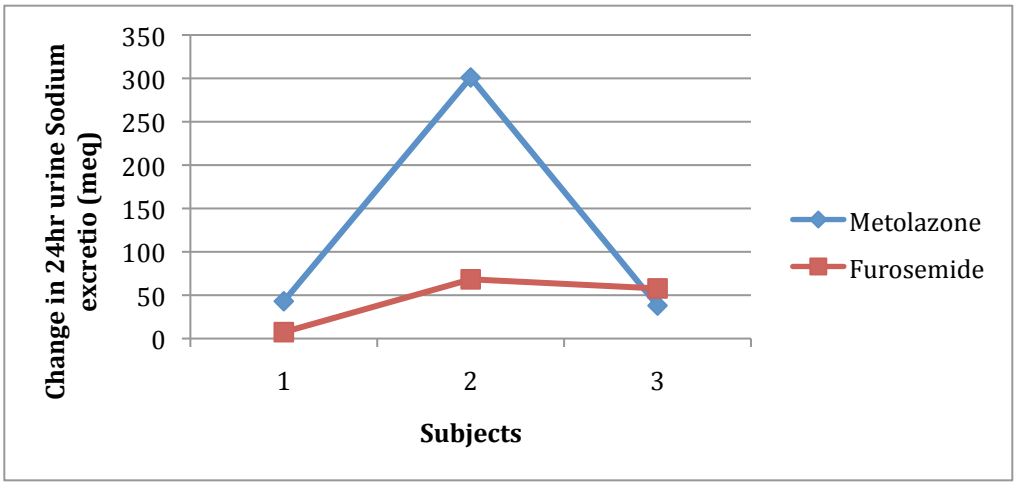

Figure 1: Change in 24hr urinary sodium excretion. Group 1- Metolazone & Group 2- Furosemide

Subject 4 requested immediate paracentesis after consenting to participate. Since we could not collect more data he was excluded from further analysis. Outcomes measures are summarized in Table 2. The mean increase in 24-hour urine sodium excretion with Group 1 was 127.3 meq (range 38-301 meq) while for Group 2 it was 44.5 meq (range 7.4-68 meq). Metolazone produced approximately 3 times greater increase in urine sodium excretion then additional dose of furosemide but the results were not statistically significant (p=1.0, figure 1).

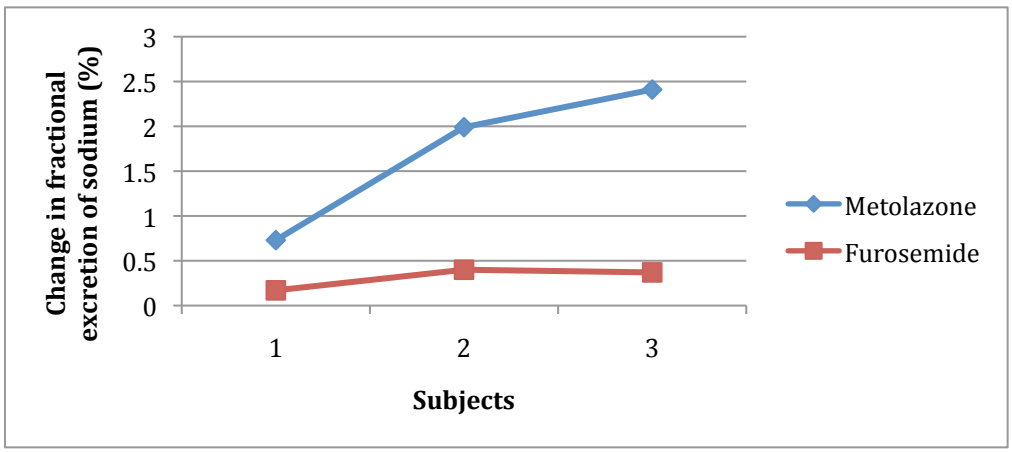

Figure 2: Change in fractional excretion of sodium. Group 1- Metolazone & Group 2- Furosemide

The baseline doses of diuretics in the two groups were different and clinically relevant although not statistically different. The baseline dose of diuretics will influence the baseline sodium excretion of groups respectively. Multivariate analysis adjusting for baseline sodium excretion showed no association between baseline sodium excretion and outcome i.e. changes in 24 hr urinary sodium excretion (p=0.13). Multivariate model adjusting for all co-variates like age, MELD score, dose of furosemide and spironolactone was not done as with a sample size of 6 assumptions for these analysis are violated. Since this can affect urinary sodium excretion, multivariate analysis adjusting for baseline dose of diuretics was done. There was marked increase in fractional excretion of sodium for group 1 as compared to Group 2 (mean change of 1.71±0.87% for Group 1 vs. 0.31±0.13% for Group 2, Figure 2). Similarly urine output increased for both groups but it was more then 3 times greater for Group 1 as compared to Group 2 (1513±1178 ml vs. 457±489 ml, figure 3). Both sodium excretion and urine output showed a marked increase with metolazone as compared to furosemide The changes in these indices with metolazone are clinically relevant. However, they are not statistically significant most likely because with the sample size in this pilot study was insufficient. We had originally estimated a sample size of 10 in each group to be adequate to show a significant difference.

	24h urine Sodium		Urine Volume		FENA	
	Before	After	Before	After	Before	After
Group 1	meq/day	meq/day	litres/day	ml/day	%	%
1	60	103	0.9	1.3	0.7	1.4
2	48	349	1.4	2.9	0.1	2.1
3	84	122	2.9	5.6	0.9	3.4
Mean±SD	64±18	191±136.9	1.8±1.1	3.3±2.2	0.6±0.5	2.3 ±1.0
Median	60	122	1.4	2.9	0.7	2.1
Group 2						
5	14.6	22	0.5	0.5	0.1	0.27
6	11.7	80	2.3	2.6	0.04	0.44
7	7.21	65	1	2.1	0.05	0.42
Mean±SD	11.2±3.7	55 ±30	1.3±0.9	1.7±1.1	0.06±0.03	0.38±0.09
Median	11.7	65	1	2.1	0.05	0.42

Table 2: Summary of outcome measures in the two groups. FENA – fractional excretion of sodium

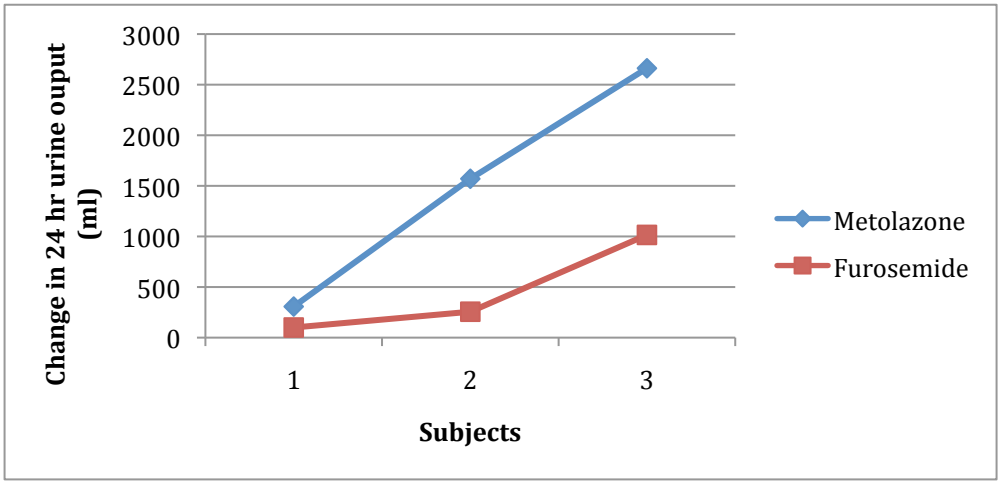

Figure 3: Change in 24hr urine output. Group 1- Metolazone & Group 2-Furosemide

There was fall in creatinine clearance by 18ml/min in the metolazone group as compared to 9.7 ml/ min in the furosemide group and although this was not significantly different (p=0.4, Table 3) it deserves further study. There was no appreciable change in pre and post diuresis serum sodium concentration in the two groups. Subject 7 had an initial serum potassium concentration of 3.6 meq/l and decreased to 2.8 meq/dl. Hypokalemia was corrected with oral potassium supplementation. Other subjects showed no appreciable change in serum potassium concentration. There was no relevant change in blood pressure and other hemodynamic indices.

	Plasma Sodium		Plasma Potassium		Creatinine clearance	
	Before	After	Before	After	Before	After
Group 1	meq/liter	meq/liter	meq/liter	meq/liter	ml/min	ml/min
1	139	135	4.8	4.8	42	38
2	132	131	3.8	4.1	122	96
3	137	134	3.9	4.9	128	104
Mean ± SD					97 ±48	79 ± 36
Median					122	96
Group 2						
5	133	130	3.5	4.8	75	68
6	131	128	4.2	4.1	121	99
7	134	132	3.6	2.8	81	81
Mean ± SD					92 ±25	82 ±16
Median					81	81

Table 3: Results of serum electrolytes and creatinine clearance

Chapter 4

Discussion

Metolazone is used commonly in refractory fluid overload states such as congestive heart failure and nephrotic syndrome (14-16). However there is limited information regarding its efficacy as a combination diuretic in cirrhotics (19, 20). The results of our pilot study showed that adding oral metolazone could increase urinary sodium excretion without major adverse effects. Subjects in metolazone group increased their urinary sodium excretion by approximately 3 times more than those who received additional dose of furosemide (127 meq / day versus 44 meq/day). This was accompanied by increase in urine output leading to fluid mobilization. However results were not significant because the planned sample size was not achieved.

Metolazone is commonly used synergistically with furosemide in many fluid overload states. It acts on the luminal surface of both proximal and distal convoluted tubule (21-23). Spironolactone and furosemide block sodium reabsorption at the collecting and thick ascending loop of Henle respectively. When metolazone is added to this regimen it leads to a sequential inhibition of sodium reabsorption due to its unique property of action at the proximal tubule (24). This results in more effective natriuresis. This is the basis of its efficacy in many fluid overload states including cirrhosis.

Refractory ascites still remains a management dilemma. The existing treatment options are expensive and invasive. Recently there have studies showing use of midodrin, clonidine and hypertonic saline with high dose furosemide in refractory ascites but none of them have been validated and near to be put in practice (25-27). On the other hand, metolazone is already being used in refractory fluid overload states such as congestive heart failure and nephrotic syndrome and is a potential option in cirrhotics with refractory ascites.

Our pilot study in a limited number of subjects showed 10 mg of metolazone was adequate dose for increasing diuresis in refractory ascites. In the absence of dose escalation studies this dose was selected based on a single prior study. All three subjects showed a good diuretic response with

this dose of metolazone and there were no major complications although further studies are needed to verify safety. This study also added clinical data regarding the variability of response.

One of the criteria for defining refractory ascites is use of maximum dose of diuretics (i.e. 400 mg of spironolactone and 160 mg of furosemide). All subjects in our study were requiring repeated paracentesis for their control of their ascites but none of them was even close to these diuretic doses. Other studies have cited similar experience and it is unusual to reach these high doses of diuretics without experiencing side effects (28). We think adding metolazone to lower doses of spironolactone and furosemide will lead to more and safer diuresis then increasing the dose of furosemide and spironolactone to these high levels.

The main limitation of this study is that the data is with a single dose of metolazone. It will require more data with prolonged use of metolazone to establish safety in cirrhotics. The other drawback is that some baseline clinical characteristics were not comparable in the two groups. Treatment was randomized but it is difficult to get even distribution of confounding factors in the groups with such a small sample size. Although multivariate analysis did not show any affect of these on the outcome, study with larger sample size is needed.

Our enrollment rate was low i.e. around 20%. Many eligible subjects with refractory ascites had on-going medical issues like spontaneous bacterial peritonitis, gastrointestinal bleeding or altered mental status at the time of hospitalization that prevented enrollment. We attempted to enroll them after discharge but many could not be contacted while others cited transportation issues. Some subjects had labile kidney function and were not enrolled due to safety concerns. A minority had personal reservations and did not want to enroll. There were many eligible subjects with refractory ascites in TDCJ system but conducting a study amidst heavy clinical responsibilities in the prison hospital was a logistic issue. These subjects could not be brought over to the clinical research center for study purpose due to inadequate number of security personnel's.

The major purpose of this pilot study was to see if metolazone, when given to patients with refractory ascites would have a substantial effect size and secondarily one that is compare it to that seen with current conventional therapy, which is to increase the dose of furosemide. Our observation of a

substantial effect of metolazone is somewhat compromised because baseline sodium excretion was different in the two groups. This difference was not statistically significant, and since treatment was randomized and the sample size was small there is no reason to think that this difference was not due to chance. However, depending on the design of future studies it may be necessary to carry out additional pilot observations to better estimate the metolazone effect size over a wider range of baseline sodium excretion. Such additional pilot observations on metolazone effect size might not need to include a comparison with an increased dose of furosemide, since studies that compare two treatments and aim to achieve statistical significance generally require a large sample size and are not considered pilot studies. Other option will be a cross over study design where each subject will get both treatments with intervening wash out period. In this type of design each subject will serve as its own control and thus reduce the required sample size.

This pilot project provides proof of concept that metolazone when added to a conventional diuretic regimen can lead to increased natriuresis. It can be an option for diuretic refractory patients as an alternative to more invasive procedures. However, this will require larger randomized study to provide the evidence required to alter accepted management practice.

Appendix A

Data Abstraction Form

Unique Pt identifier:

Age:

Sex:

Race:

Etiology of liver disease:

MELD score:

Date of study:

Furosemide dose:

Spironolactone dose:

Group Randomization:

Adverse effects:

Group	Before	After
24hr urine sodium		
24hr urine output		
Fractional excretion of sodium		
Weight		
Serum sodium		
Serum potassium		
Creatinine clearance		

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VITA

Sahil Mittal was born in Patiala, India on September 21st, 1976 to Veena Mittal and Dr P.K.Mittal. He obtained his MBBS (Bachelor of Medicine, Bachelor of Surgery) from Government Medical College, Patiala in 2001. He earned his MD (Doctorate in Medicine) at the prestigious Postgraduate Institute of Medical Education and Research, Chandigarh in 2005. His medical training in US began as resident in Internal Medicine at the University of Texas Medical Branch, Galveston in 2006. Subsequently he began his fellowship in Gastroenterology and Hepatology at the same institution in 2009. His formal training in clinical research in pursuit of a Masters of Science in Clinical Investigation began in 2010. Future goals include clinical activity and outcomes research in gastroenterology and hepatology.

Permanent address:
2622 Pine Street,
Galveston,
Texas, 77551

This thesis was typed by Sahil Mittal.