Original Article

Prevalence of Thiamine Deficiency in Heart Failure Patients on Long-term Diuretic Therapy

Shrenik Doshi, T. Velpandian[1], Sandeep Seth, S. K. Maulik[2], Balram Bhargava, Vinay K. Bahl

Departments of Cardiology, [1]Ocular Pharmacology and Pharmacy and [2]Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background: Loop diuretics are an integral part of heart failure management. It has been shown that loop diuretics cause thiamine deficiency (TD) by increasing its urinary loss. The aim of this study was to determine the prevalence of TD in heart failure patients on long-term oral loop diuretics. **Methods:** Heart failure patients (cases) on oral loop diuretics (furosemide ≥40 mg/day or torsemide ≥20 mg/day), irrespective of the cause of heart failure, were compared to non-heart failure patients (controls) not on loop diuretics in a 1:1 ratio. Whole blood free thiamine level was determined by liquid chromatography-tandem mass spectrometry method. **Results:** A total of 100 subjects were enrolled in a 1:1 ratio (50 cases and 50 controls). 67% of the total study population had TD, (defined as whole blood free thiamine level <0.7 ng/ml). There was no difference in mean thiamine level between cases and controls. On comparing patients with TD in both groups, patients on diuretics had significantly lower thiamine level compared to the patients, not on diuretics ($P < 0.0001$). **Conclusions:** There was no difference in the thiamine level when patients on loop diuretics were compared to controls. However, very low thiamine levels (<0.1 ng/ml) was significantly more common in patients on loop diuretics.

Key words: Loop diuretics, heart failure, India, thiamine deficieny

Introduction

Thiamine deficiency (TD) largely manifests as neurologic (dry beriberi) or cardiovascular disease. Cardiovascular manifestation of TD includes peripheral vasodilation leading to high-output cardiac failure (wet beriberi), biventricular low-output failure, and retention of sodium and water, resulting in edema. Therefore, TD would be expected to worsen symptoms in the setting of established congestive heart failure (CHF).[1] Loop diuretics are routinely used for management of symptoms of heart failure.[2] In addition to the other documented side effects of loop diuretics, the possibility of TD is of particular interest due to its possible cardiovascular consequences. The loop diuretic furosemide has been shown to induce TD in experimental animals and in patients with CHF.[3-5] The probable mechanism suggested is increased urinary loss of thiamine caused by the diuretic, or an inadequate dietary intake.[3,6] It is possible that in patients receiving long-term loop diuretics therapy, TD could be one of the determinants of their poor clinical status. Therefore, the objective of this study was to assess the prevalence of TD in CHF patients receiving long-term loop diuretic therapy.

Access this article online

Quick Response Code:

Website: www.j-pcs.org

DOI: 10.4103/2395-5414.157561

Methods

In this prospective, cross-sectional, observational study, the prevalence of TD in 50 patients with the diagnosis of heart failure (with reduced or normal ejection fraction) and receiving high-dose oral loop diuretics was determined and compared with 50 control subjects not receiving loop diuretics.

Demographic details, etiology of heart failure, New York Heart Association class at the time of enrolment, presence of any cardiac arrhythmias or heart blocks, left ventricular (LV) function, associated disease such as hypertension and diabetes and habits such as smoking, alcohol and tobacco chewing and routine blood chemistry were compared between the two groups

Inclusion criteria for cases

- Patients with heart failure requiring oral loop diuretic medicine
- Six months or more of oral loop diuretic use
- Dose of diuretics being taken by patients-Furosemide ≥40 mg/day or torsemide ≥20 mg/day
- Age between 18 and 80 years.

Exclusion criteria for cases

- Patients who decline to give consent
- Patients consuming alcohol

Address for correspondnce: Dr. Shrenik Doshi, Department of Cardiology, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-Mail: shrenik421@gmail.com

- Severe renal or liver disease
- Prolonged diarrhea
- Acute infection.

Control subjects were patients without heart failure on follow-up in cardiology outpatient department and not receiving loop diuretics, in a 1:1 ratio. Control subjects were excluded if they had any known condition that may affect thiamine status or were taking thiamine-containing supplements. Approval for this study was obtained from the Institutional Ethics committee.

Blood collection and storage

A volume of 5 ml blood was withdrawn and stored in (ethylene-diamine-tetraacetic acid) vacuette at −20°C. Whole blood thiamine level was determined using liquid chromatography tandem mass spectrometry method.

Normal whole blood free thiamine level

Normal free and total thiamine level for Indian population is not available. In a study of healthy Japanese adults ($n = 1069$), normal whole blood free thiamine level obtained was 0.7−6.1 ng/ml (2–18 nmol/l).[7] Based on this study, we defined TD as whole blood thiamine level <0.7 ng/ml.

Statistical analysis

Differences between mean values were analyzed by Student's unpaired *t*-test for those with a normal distribution and by Mann–Whitney U-test for those without a normal distribution. To compare proportions, Chi-square test/Fisher's exact test was used. A two-tailed $P < 0.05$ was considered statistically significant. SPSS statistics version 17 (SPSS Inc., IL, USA) was used for analysis.

Results

Of the total patients screened, 50 cases (patients on diuretics) and 50 controls (patients not on diuretics) were enrolled for the final analysis [Figure 1]. Table 1 shows the baseline characteristics of the study population.

As seen in Table 1, cases were significantly younger than controls with equal sex distribution. Among patients on loop diuretics, furosemide equivalent dose ranged from 40 to 140 mg/day, mean 55.60 ± 28.93 mg/day. Furosemide equivalent dose of torsemide was calculated by doubling the torsemide dose.[8] There was no significant difference in the diuretic dose among patients with and without TD (mean furosemide equivalent dose 51.6 ± 27.7 mg/day versus 57.9 ± 34.5 mg/day, respectively; $P = 0.50$). Associated conditions such as diabetes, hypertension, dyslipidemia and smoking were more common among controls then cases.

When the blood investigations were compared between the two groups [Table 2], heart failure patients had significantly lower hemoglobin content while blood urea and serum bilirubin levels were significantly higher compared to the control population. With regards to whole blood thiamine levels, when a cut-off of 0.7 ng/ml was used as lower limit of normal, 67% of the total study population had TD. When the two groups were compared, there was no significant difference in the mean thiamine levels between

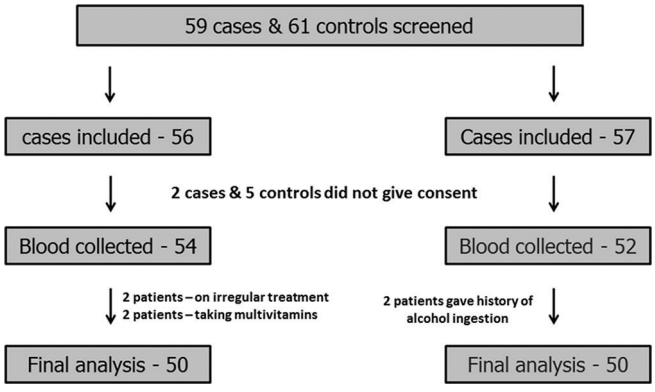

Figure 1: Study flow chart.

Table 1: Baseline characteristics of patients receiving diuretics (cases) and not receiving diuretics (controls)

Characteristics	*n*=50	
	Cases	Controls
Age (years)	42.74±13.21	53.20±13.47
Sex		
Male	26	25
Female	24	25
Diagnosis		
DCMP	27	00
ICMP	06	00
CAD	02	42
Valvular heart disease	11	02
Others	04	06
NYHA class		
NYHA I	02	11
NYHA II	21	25
NYHA III	23	14
NYHA IV	04	00
LVEF (%)	32.12±15.62	52.7±11.12
Furosemide equivalent diuretic dose/day	55.60±28.93	-
Drugs		
Loop diuretics	50	00
Spironolactone	43	01
Digoxin	21	01
Beta blockers	32	47
ACEI/ARB	34	22
Nitrates	09	42
Aspirin	11	45
Clopidogrel	06	31
Oral anticoagulant	04	01
Associated conditions		
Diabetes mellitus	08	15
Hypertension	06	29
Dyslipidemia	01	16
Smoking	06	11

DCMP: Dilated cardiomyopathy, ICMP: Ischemic cardiomyopathy, CAD: Coronary artery disease, NYHA: New York Heart Association, LVEF: Left ventricular ejection fraction, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker

the two groups. On comparing thiamine levels in patients with TD, the mean thiamine level in cases was significantly lower as compared to controls ($P < 0.0001$) [Figures 2-4].

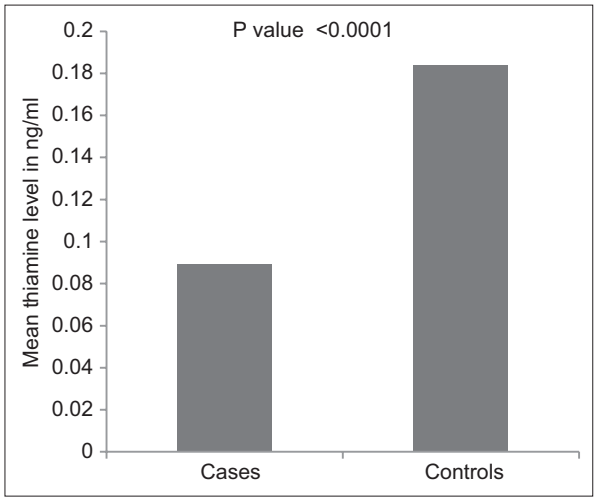

Figure 2: Comparison of thiamine levels in patients with thiamine deficiency.

When patients with normal thiamine levels in both the groups were compared, there was no significant difference between the mean thiamine levels [Table 3]. Among patients without TD, the thiamine levels in patients on diuretics was inhomogeneous compared to patients not on diuretics [Figure 5].

Table 2: Blood investigations

Characteristics	*n*=50		*P*
	Cases	Controls	
Hemoglobin (g%)	12.56±1.74	13.81±1.80	<0.0001
Serum creatinine (mg%)	1.04±0.27	1.01±0.21	0.79
Blood urea (mg%)	33.12±12.30	27.28±6.54	0.01
Serum Na^+(mmol/L)	133.84±5.29	137.98±4.65	0.94
Serum K^+(mmol/L)	4.25±0.37	4.27±0.38	0.80
Serum bilirubin (mg/dl)	1.02±0.49	0.82±0.28	0.01
SGOT (U/L)	33.82±21.34	30.26±10.23	0.95
SGPT (U/L)	37.6±31.75	30.12±9.16	0.75
Serum uric acid (mg/dl)	5.99±1.56	5.53±1.45	0.09

Na^+: Sodium; K^+: Potassium, SGOT: Serum glutamic oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase

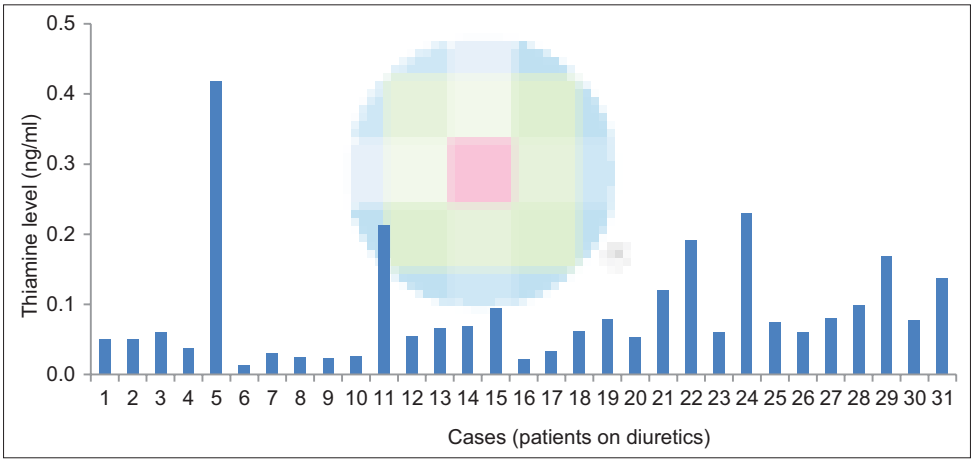

Figure 3: Thiamine levels in cases with thiamine deficiency (i.e., thiamine <0.7 ng/ml).

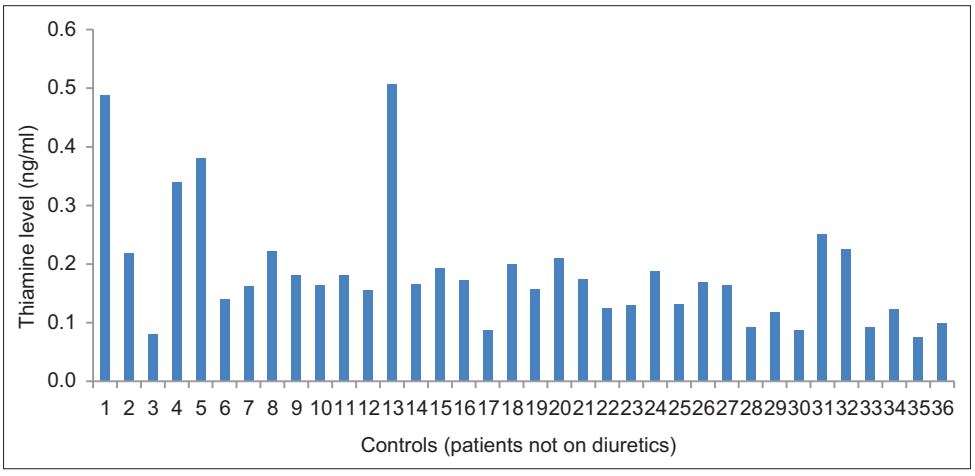

Figure 4: Thiamine levels in controls with thiamine deficiency (i.e., blood thiamine level <0.7 ng/ml).

Discussion

Normal reference whole blood thiamine level (free or total) of Indian population is not available. Considering the thiamine level of healthy Japanese adults to be a reference standard (0.7−6.1 ng/ml),[7] 67% of our study population suffered from TD. Consumption of polished rice and lack of food fortification with thiamine could be the possible reasons for such significant prevalence of TD.

When heart failure patients with diuretics were compared with non-heart failure patients without diuretics, there was no significant difference in the mean thiamine concentration between the two groups. This was contrary to previous studies showing loop diuretic-induced significant TD.[3,6,9,10] However, all these studies used erythrocyte transketolase enzyme activity as a surrogate marker of TD rather than direct measurement of thiamine levels by high-performance liquid chromatography (HPLC). Transketolase is less sensitive than HPLC, has poor precision, and specimen stability concerns.[11] Studies using direct measurement of blood thiamine levels, as used in our study, have failed to show diuretic-induced TD. Härdig *et al.*,[12] compared 41 elderly patients taking furosemide (at least 60 mg/day) with 34 healthy elderly (mean age 78 years vs. 79 years). There was no difference in the whole blood thiamine or thiamine pyrophosphate levels, measured by HPLC, between the two groups. Similarly, Yue *et al.*,[13] also showed no difference in the thiamine levels, measured by HPLC, between patients on diuretics compared to those, not on diuretics.

Table 3: Thiamine levels

Characteristics	Cases	Controls	Remarks
Whole blood thiamine level (mean, ng/ml)	1.02±1.65	0.60±0.78	*P*=0.11
	(*n*=50)	(*n*=50)	
Patients without TD (thiamine level >0.7 ng/ml)			
Number of patients	19/50	14/50	33/100
Whole blood thiamine level (mean, ng/ml)	2.55±1.86	1.68±0.73	*P*=0.24
Patients with TD (thiamine level <0.7 ng/ml)			
Number of patients	31/50	36/50	67/100
Whole blood thiamine level (mean, ng/ml)	0.089±0.082	0.184±0.101	*P*<0.0001

TD: Thiamine deficiency

One mechanism for the apparent lack of diuretic-induced TD could be the development of diuretic resistance on chronic use. In other words, on prolonged diuretic use, a steady state is achieved as a result of Na^+ and Cl^- reabsorption, resulting in reduced urine output – and thus reducing urinary thiamine excretion. Another explanation could be over the counter consumption of multi-vitamin pills without the knowledge of the treating physician. The thiamine levels in patients on diuretics are inhomogeneously distributed compared to the homogenous distribution in the control population, both in patients with normal and low thiamine levels [Figures 3-5].

There was no significant difference in the mean thiamine level between cases and controls without TD. When subjects with TD (i.e., thiamine level <0.7 ng/ml) were compared, the mean thiamine level in patients on diuretics was significantly lower than in patients without diuretic intake ($P < 0.0001$). Of the 31 cases with TD, 24 patients had thiamine level <0.1 ng/ml; whereas of the 36 controls with TD, only 6 patients had thiamine level <0.1 ng/ml ($P < 0.0001$) [Figure 6]. Either the normal reference whole blood thiamine level for the Indian population is different and a significant number of controls with thiamine value >0.1 ng/ml are falsely labeled as thiamine deficient; or those patients who do not develop diuretic resistance continue to have high urinary thiamine loss leading to very low thiamine levels.

Few studies have demonstrated an increase in LV ejection fraction upon thiamine supplementation in heart failure patients receiving loop diuretics.[3,10,14] If studies which have showed that loop diuretics do not cause TD are to be believed then the theory of thiamine supplementation-induced improvement

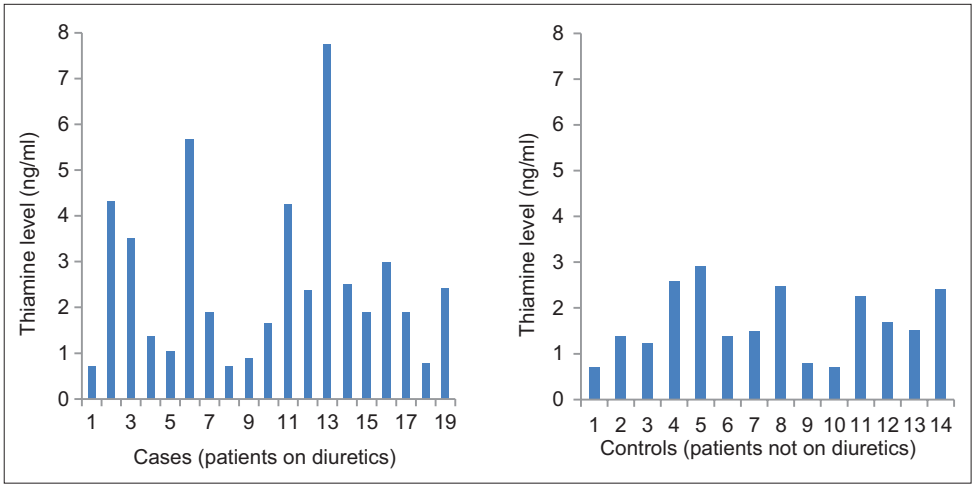

Figure 5: Thiamine levels in cases and controls without thiamine deficiency (thiamine >0.7 ng/ml).

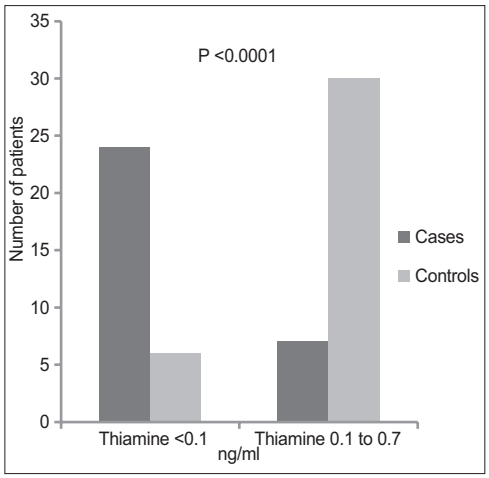

Figure 6: Number of cases with very low thiamine levels were significantly more among cases compared to controls.

in LV ejection fraction becomes questionable. However, the fact that diuretics do not cause TD but still thiamine supplementation improves LV function in patients receiving diuretics can be explained by the study of Zangen *et al.*,[15] which showed that furosemide inhibits thiamine uptake in cardiac cells, the effect being dose dependent.

Study limitations

In the presence of baseline TD, it is difficult to demonstrate diuretic-induced TD. There are several limitations of the current study. First of all, control arm consisting of healthy normal subjects should have been included to define the normal reference thiamine value for comparison. Such control arm would also have helped in defining the normal whole blood thiamine level in Indian population. Second limitation is a lack of urinary thiamine estimation which would have helped in differentiating cases (patients on diuretics) with TD to be secondary to diuretic-induced increased urinary loss from true nutritional TD. Other limitation is that we measured whole blood free thiamine levels instead of total thiamine levels or thiamine diphosphate levels. Free thiamine constitutes only 10% of the total thiamine in whole blood, 80% of the latter is thiamine diphosphate. Finally, simultaneous measurement of transketolase activity could have helped in differentiating controls with TD into two groups – those with true TD versus those with sub-clinical TD.

Conclusions

Two-third of our study population (including controls) was thiamine deficient. Use of par-boiled rice in place of polished rice and food fortification with thiamine would be the cornerstone to prevent this deficiency. Furthermore, a study to define normal thiamine level in the Indian population is required. Our study did not show a significant difference in the thiamine level between heart failure patients on diuretics compared to patients not receiving diuretics. Among patients with TD, the prevalence of very low thiamine levels (<0.1 ng/ml) was significantly more common in patients receiving diuretics. The exact mechanism of this is not clear, but it could probably indicate effectiveness of a diuretic medication (or in other words lack of diuretic resistance). Whether control population with TD is truly deficient needs to be judged either by simultaneous thiamine diphosphate measurement or by comparing it with healthy volunteers.

References

1. Gubler CJ. Thiamin. In: Machlin LJ, editor. Handbook of Vitamins. 2nd ed. New York, NY: Marcel Dekker; 1991. p. 233-81.
2. Advisory Council to Improve Nationwide Outcomes in Heart Failure (ACTION HF). Recommendations for the treatment of chronic heart failure. Am J Cardiol 1999;83:S1-38.
3. Seligmann H, Halkin H, Rauchfleisch S, Kaufmann N, Motro M, Vered Z, *et al.* Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: A pilot study. Am J Med 1991;91:151-5.
4. Yui Y, Itokawa Y, Kawai C. Furosemide-induced thiamine deficiency. Cardiovasc Res 1980;14:537-40.
5. Pfitzenmeyer P, Guilland JC, d'Athis P, Petit-Marnier C, Gaudet M. Thiamine status of elderly patients with cardiac failure including the effects of supplementation. Int J Vitam Nutr Res 1994;64:113-8.
6. Brady JA, Rock CL, Horneffer MR. Thiamin status, diuretic medications, and the management of congestive heart failure. J Am Diet Assoc 1995;95:541-4.
7. Ihara H, Hirano A, Wang L, Okada M, Hashizume N. Reference values for whole blood thiamine and thiamine phosphate esters in Japanese adults. J Anal Biosci 2005;28:241-6.
8. Cleland JG, Coletta A, Witte K. Practical applications of intravenous diuretic therapy in decompensated heart failure. Am J Med 2006;119 12 Suppl 1:S26-36.
9. Zenuk C, Healey J, Donnelly J, Vaillancourt R, Almalki Y, Smith S. Thiamine deficiency in congestive heart failure patients receiving long term furosemide therapy. Can J Clin Pharmacol 2003;10:184-8.
10. Shimon I, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, *et al.* Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. Am J Med 1995;98:485-90.
11. Herve C, Beyne P, Lettéron P, Delacoux E. Comparison of erythrocyte transketolase activity with thiamine and thiamine phosphate ester levels in chronic alcoholic patients. Clin Chim Acta 1995;234:91-100.
12. Härdig L, Daae C, Dellborg M, Kontny F, Bohmer T. Reduced thiamine phosphate, but not thiamine diphosphate, in erythrocytes in elderly patients with congestive heart failure treated with furosemide. J Intern Med 2000;247:597-600.
13. Yue QY, Beermann B, Lindström B, Nyquist O. No difference in blood thiamine diphosphate levels between Swedish Caucasian patients with congestive heart failure treated with furosemide and patients without heart failure. J Intern Med 1997;242:491-5.
14. Schoenenberger AW, Schoenenberger-Berzins R, der Maur CA, Suter PM, Vergopoulos A, Erne P. Thiamine supplementation in symptomatic chronic heart failure: A randomized, double-blind, placebo-controlled, cross-over pilot study. Clin Res Cardiol 2012;101:159-64.
15. Zangen A, Botzer D, Zangen R, Shainberg A. Furosemide and digoxin inhibit thiamine uptake in cardiac cells. Eur J Pharmacol 1998;361:151-5.

How to cite this article: Doshi S, Velpandian T, Seth S, Maulik SK, Bhargava B, Bahl VK. Prevalence of thiamine deficiency in heart failure patients on long-term diuretic therapy. J Pract Cardiovasc Sci 2015;1:25-9.

Source of Support: Nil. **Conflict of Interest:** None declared.