

**PREVALENCE AND MANAGEMENT OF DIURETIC INDUCED MUSCLE CRAMPS IN  
A TERTIARY CARE HOSPITAL: A PROSPECTIVE STUDY****Ann Mary George\*, Aiswarya Santhosh, Anjaly Augustine, Soumya Jose and Deepthi C. Denny**

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**ABSTRACT**

Cramps occurred in the course of diuretic therapy are due to electrolyte disturbances. Common causes of muscle cramps include hyponatremia, hypokalemia, hypomagnesaemia, hypercalcemia, increased age, neurological disease, peripheral vascular disease, arthritis and hemodialysis. A prospective observational study was conducted for assessing the prevalence and management of diuretic induced muscle cramps. A total of 104 patients were enrolled for the study who had a history of diuretic use for at least 3 months, their medical and medication profiles were assessed and questionnaires filled through direct interview with the patient. The prevalence of muscle cramps was 18.26% and Vitamin E (46.15%) was frequently prescribed to relieve cramps. This study also points out the association between muscle cramps and hyponatremia which was found significant ( $P$  value= 0.025) when statistical analysis was performed using Chi-Square test.

**INTRODUCTION**

Diuretics are the drugs which cause a net loss of sodium and water in urine. They are also known as natriuretics or waterpills. Diuretics are most commonly used for management of edematous conditions (fluid retention), high blood pressure, glaucoma, nephrogenic diabetes insipidus.<sup>[1]</sup> The diuretic effect of different classes of diuretic varies considerably with the increase in  $\text{Na}^+$  secretion varying from less than 2% for the weak potassium sparing diuretics to over 20% for the potent loop diuretics. When the body excretes excess fluid and sodium, potassium is also losing from body in this process, which plays a vital role in proper muscle function. If the potassium level is deficient, it can cause not only cramps but also muscle weakness and fatigue, according to the Linus Pauling Institute at Oregon State University.<sup>[19]</sup> Thus volume contraction appears to be the one mechanism that is common to all classes of diuretics.<sup>[10]</sup>

The management of diuretic-associated cramps include preventing and correcting electrolyte imbalances, and avoiding profound volume contraction. Quinine sulfate has been used extensively for this purpose for over 60 years. Other medications that have been used to treat cramps include vitamin B, vitamin E, verapamil, gabapentin, nonsteroidal anti-inflammatory drugs, and diphenhydramine. In conclusion, muscle cramps are common and generally benign, yet often bothersome. Their etiology is unclear, and an association with diuretic agents is possible.

This study assesses the prevalence and management of diuretic induced muscle cramps, and also the severity of muscle cramps associated with diuretic therapy.

**MATERIALS AND METHODS**

A prospective observational study was conducted with 104 adult in-patients who had a history of diuretic use for at least 3 months. All data such as demographic details, past medical and medication history and lab investigations were collected from the patient's medical records and documented on a standard data entry form. A questionnaire was also completed by direct interview method for assessing the severity and frequency of muscle cramps. In this study, visual analogue scale in cramp questionnaire was used to measure the severity of pain associated with muscle cramps. V symptom score(CSS) was calculated for finding out the clinically significant cramps. Statistical analysis is done using parametric Chi square method and  $P$  value was estimated.

**RESULT**

The current study has assessed a total of 104 patients with history of diuretic use for at least 3 months. During the study period of 6 months, the prevalence and management of diuretic induced muscle cramps and their severity and frequency were assessed. This study highlights the prevalence (18.26%) of muscle cramps in adult patients in the age group 65-75 and describes the various characteristics such as location (more in calf), duration (lasting several minutes in all patients), severity

of associated pain (47.36% had 3 on the 0-5 scale), prevalence of clinically significant cramps (57.89% had CSS  $\geq 9$ ), and association of CSS score with sodium levels (P value = 0.025). Statistical analysis was performed using Chi-Square test and P value estimated. Furthermore, in this study calcium supplements (30.76%), vitamin D (23.07%) and vitamin E (46.15%) supplements are prescribed for the relief of cramps of which vitamin E (46.15%) is the most common.

#### AGEWISE DISTRIBUTION OF PATIENTS

Table 1: Distribution based on age (n= 104).

Age	No. Of patients	Percentage (%)
25-35	1	0.96
35-45	4	3.84
45-55	7	6.73
55-65	14	13.46
65-75	78	75.0

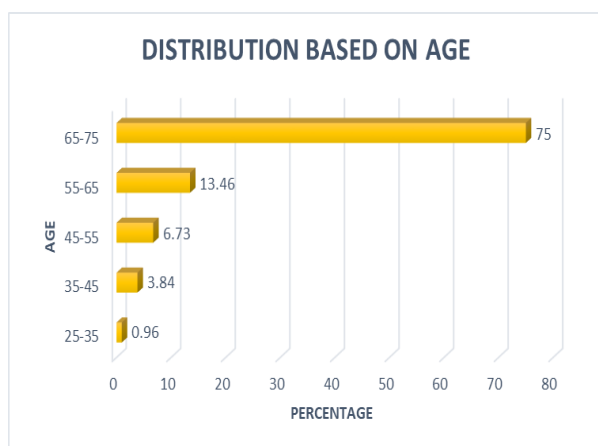


Figure 1: Distribution based on age. (n= 104).

#### GENDERWISE DISTRIBUTION OF PATIENTS WITH MUSCLE CRAMPS

Table 2: Distribution based on gender in patients with muscle cramps (n=19).

Gender	No. of Patients	Percentage (%)
Male	8	42.10
Female	11	57.89

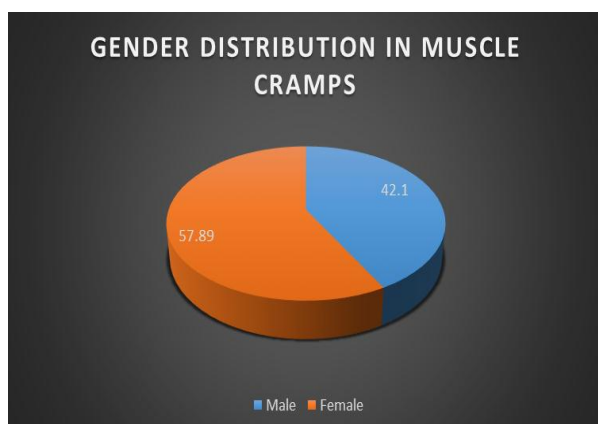


Figure 2: Distribution based on gender in patients with muscle cramps (n=19).

#### DISTRIBUTION BASED ON VARIATIONS IN THE ELECTROLYTE LEVELS

Table 3: Distribution based on potassium levels in patients with muscle cramps (n=14).

Potassium Levels	No of Patients (n= 14)	Percentage (%)
Hypokalemia	3	21.42
Hyperkalemia	0	0
Normal	11	78.51

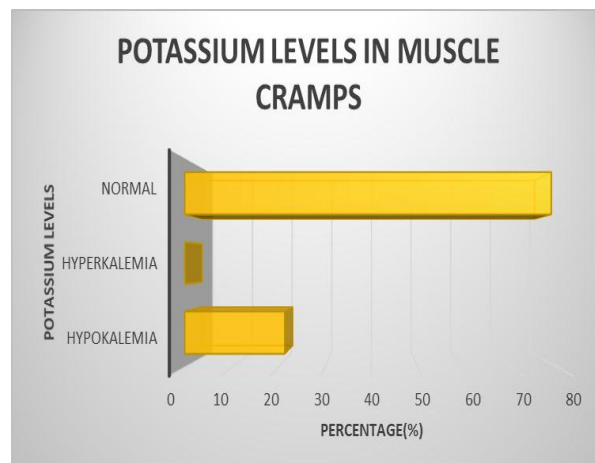


Figure 3: Distribution based on potassium levels in patients with muscle cramps (n=14).

Table 4: Distribution based on sodium levels in patients with muscle cramps (n=15).

Sodium Levels	No of Patients (n= 15)	Percentage (%)
Hyponatremia	8	53.33
Hypernatremia	1	6.66
Normal	6	40

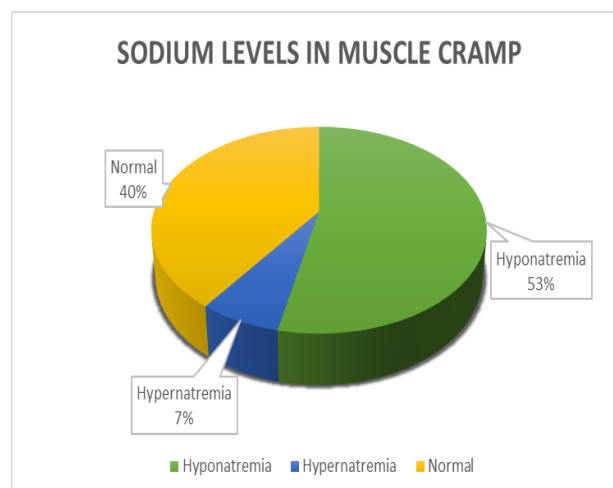
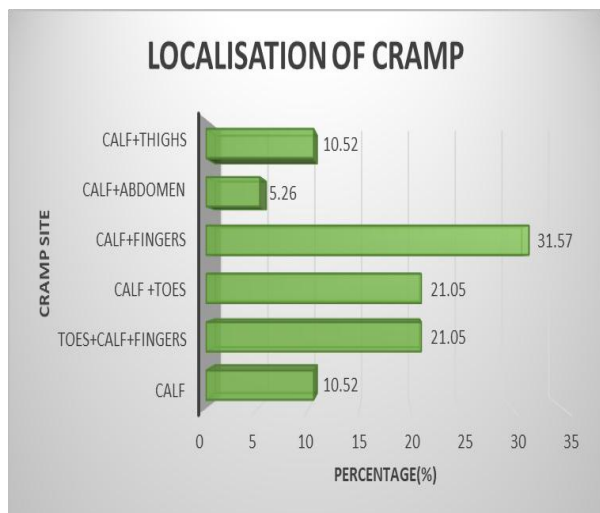


Figure 4: Distribution based on sodium levels in patients with muscle cramps (n=15).

### Distribution Based On The Localisation of Muscle Cramps

**Table 5: Distribution based on the localisation of cramp (n=19).**

Cramp Site	No.of patients	Percentage(%)
Calf	2	10.52
Toes+calf+fingers	4	21.05
Calf +Toes	4	21.05
Calf+Fingers	6	31.57
Calf+Abdomen	1	5.26
Calf+Thighs	2	10.52



**Figure 5: Distribution based on the localisation of cramp (n=19)**

### Distribution Based on Composite Symptom Score (C<sub>ss</sub>)

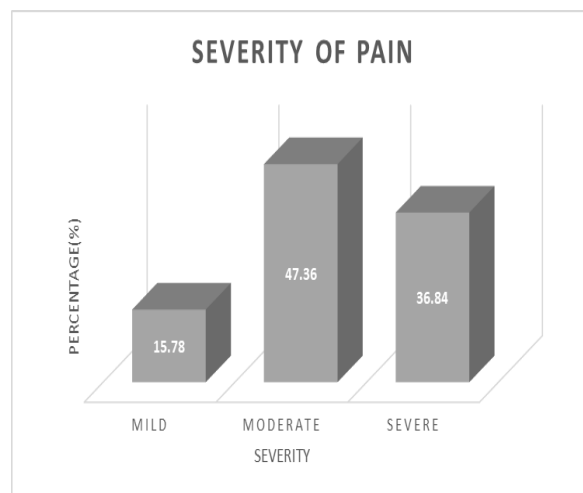
**Table 6: Distribution based on composite symptom score (n=19).**

SL.NO	Frequency (weekly)	Severity	CSS
1	3	3	9
2	4	2	8
3	3	4	12
4	3	2	6
5	4	3	12
6	3	4	12
7	2	3	6
8	3	3	9
9	4	3	12
10	3	4	12
11	3	3	9
12	2	3	6
13	2	3	6
14	3	4	12
15	1	4	4
16	3	3	9
17	3	4	12
18	2	4	6
19	4	2	8

### Distribution Based on The Severity of Pain

**Table 7: Distribution based on the severity of pain (n=19).**

Severity of Pain	No. of Patients	Percentage (%)
Mild	3	15.78
Moderate	9	47.36
Severe	7	36.84



**Figure 6: Distribution based on the severity of pain (n=19).**

### DISTRIBUTION BASED ON FREQUENCY OF MUSCLE CRAMPS

**Table 8: Distribution based on frequency of muscle cramps (n=19).**

Frequency	No.of Patients	Percentage (%)
once weekly	1	5.26
twice weekly	4	21.05
thrice weekly	10	52.63
four times a week	4	21.05

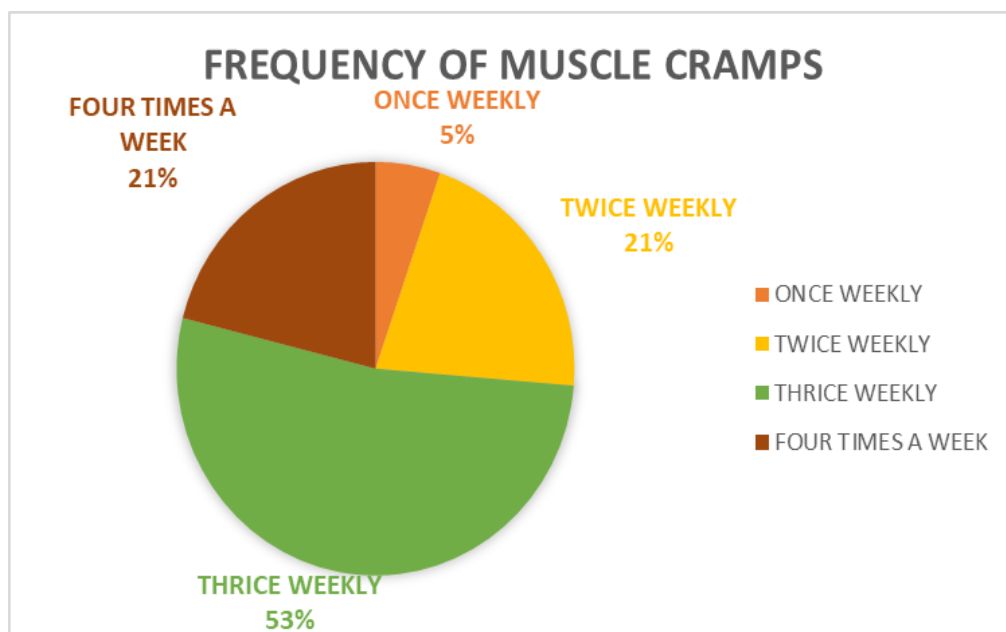


Figure 7: Distribution based on frequency of muscle cramps (n=19).

#### Distribution Based on The Treatment Of Muscle Cramps

Table 9: Distribution based on the treatment of muscle cramps (n=19).

Drugs	No.of Patients	Percentage (%)
calcium supplements	4	30.76
vitamin D	3	23.07
vitamin E	6	46.15

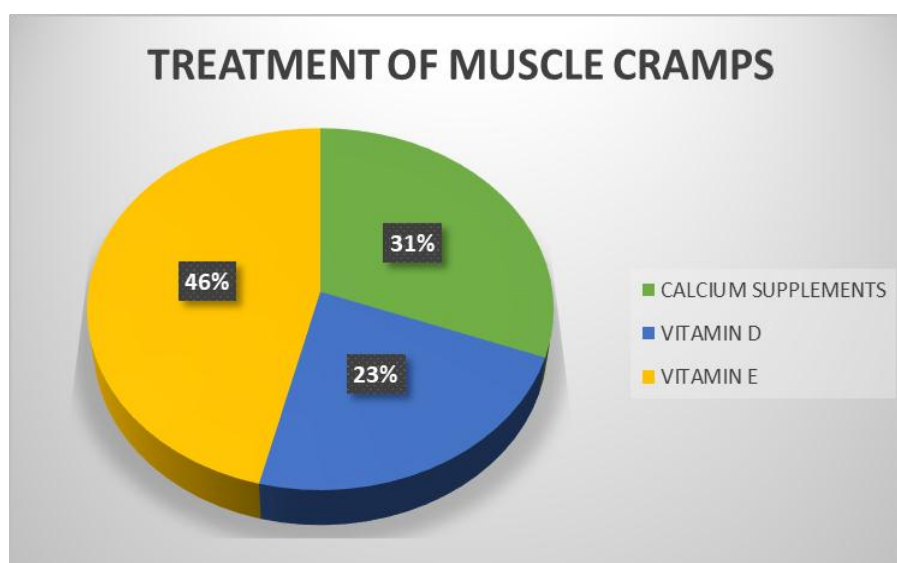


Figure 8: Distribution based on the treatment of muscle cramps. (n=19).

#### Distribution Based on Diuretic Prescribed In Patients With Muscle Cramps

Table 10: Distribution based on commonly prescribed diuretic in patients with muscle cramps.

Diuretic	No.of patients	Percentage(%)
Furosemide	8	42.10
Torsemide	5	26.31
Spironolactone+Furosemide	2	10.52
Spironolactone+Torsemide	1	5.26
Furosemide+Torsemide	2	10.52
Furosemide+Torsemide+Spironolactone	1	5.26

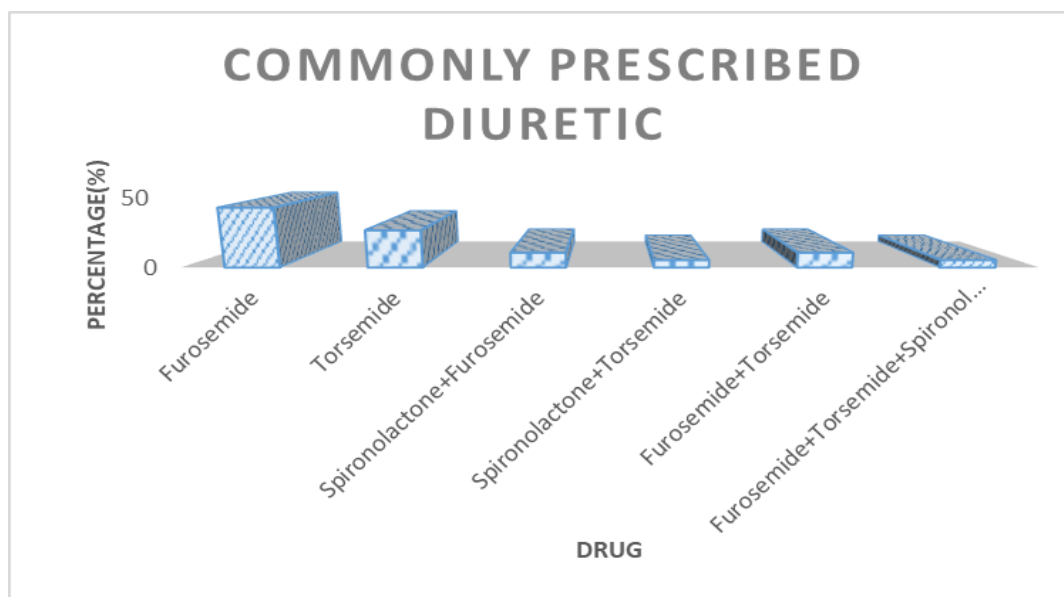


Figure 9: Distibution based on commonly prescribed diuretic in patients with muscle cramps.

#### Distribution Based On Prescribed Daily Dose Of Diuretics In Patients With Muscle Cramps

Table 11: Distribution based on prescribed daily dose of diuretics in patients with muscle cramps (n=25).

Drug	Daily dose (mg)	Frequency
Furosemide	60	1
	40	6
	20	4
	10	1
Torsemide	25	1
	20	2
	10	5
	5	1
Spironolactone	50	3
	25	1

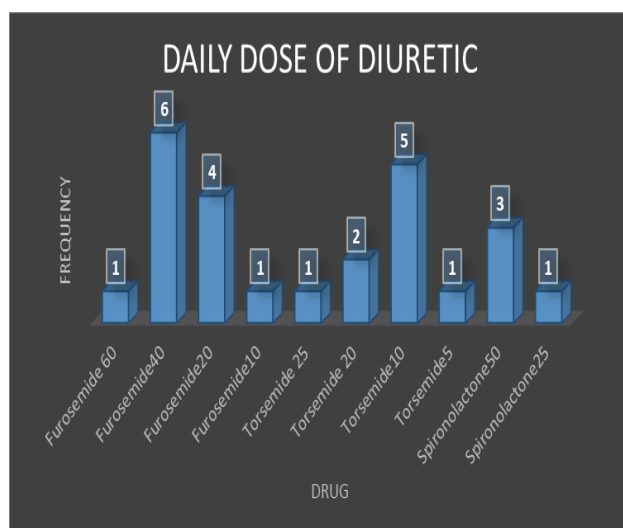


Figure 10: Distribution based on prescribed daily dose of diuretics in patients with muscle cramps (n=25).

#### STATISTICAL ANALYSIS PERFORMED USING CHI-SQUARE TEST AND P VALUE ESTIMATED

Table 12: Association of presence of muscle cramp with selected demographic variable and clinical variable.

N= 104

Sl no	Characteritics	P value	Significance
1	Age	0.483	Not significant
2	Gender	0.122	Not significant
3	Sodium level	<b>0.024*</b>	Significant
4	Potassium level	0.909	Not significant

\* Significant at 0.05 level

Table 13: Association of css score with age and sodium level

N= 104

Sl no	Symptoms	P value	Significance
1	Age	0.762	Not significant
2	Sodium level	<b>0.025*</b>	Significant

\* Significant at 0.05 level

#### DISCUSSION

In the current study, a total of 104 adult patients who had a history of diuretic use for at least 3 months were included and their demographic characteristics, past medical and medication history, electrolyte levels, comorbidities and medications used were analyzed. The respondents were grouped according to their age into 5 categories for analyzing (table 1 and figure 1). The majority of the patients (75%) comes under the category 65-75. About 13.46% patients comes under category 55-65 and 6.73% in category 45-55. Only 3.84% comes under the category 35-45 and 0.96% under the category 25-35. All individuals participated in the study (104) were grouped according to their gender for analysis, of which the respondents who actually experienced muscle cramps (19) were further grouped into 2 categories (table

2 and figure 2). Out of the 19 patients with muscle cramps, 11 are female and 8 are male.

The respondents were classified into 3 categories based on their electrolyte level (table 3, 4 and fig 3, 4). Out of the 104 patients 38.46% patients have hyponatremia, 1.92% patients have hypernatremia, 39.42% have a normal value and the sodium levels were not checked in 20.19%. Out of 104 patients, hyperkalemia was seen in 13.46%, hypokalemia was seen in 13.46%, 49.03% patients had a normal value and the potassium levels of 24.03% patients were not checked. Freidman et al showed that within 6 hours of ingesting a single hydrochlorothiazide amiloride tablet, previously affected patients had a small rise in urine osmolality and a fall in serum Na<sup>+</sup> of 5.5 meq/L.

All of the 19 patients with muscle cramps developed muscle cramps at various sites like calf, toes, fingers, abdomen and thighs (table 5 and fig 5). Majority of the patients developed muscle cramps at more than one site of which calf + fingers is the most common. Hemanth Chatrath et al conducted a study in which the lower half of the body was the most common site for muscle cramps with patients reporting in locations such as thighs (43%), calves (70%), and toes (50%).

Composite symptom score (CSS) is used to assess both the symptom frequency and severity simultaneously. CSS score is calculated by multiplying the frequency of cramps per week with the severity of cramps. Because cramps can occur at variable frequency and severity, we can define clinically significant cramps as those with CSS value greater than the median value for the study cohort. The median value of CSS score for this study is 9. A total of 11 patients have CSS score greater than the median value which indicates that they have cramps that are clinically significant (table 6). In a study conducted by Hemanth Chatrath et al there was a wide variation in the CSS score ranging from 0.3-200 with a median value of 12 in patients who reported cramps. Clinically significant cramps i.e., patients with CSS > 12 were found in 49% of patients.

In this study, visual analogue scale in cramp questionnaire was used to measure the severity of pain associated with muscle cramps. Out of the 19 patients with muscle cramp, 9 patients had moderate pain, 7 had severe pain and 3 had mild pain with muscle cramps (table 7 and fig 6). On assessing the data collected from cramp questionnaire it was observed that most of the patients developed muscle cramps thrice weekly (table 8 and fig 7), 11 patients developed muscle cramps at night and the remaining patients developed muscle cramps both at day and night. Also, all of the patients experienced muscle cramps that lasted for few minutes. A study conducted by Hemanth Chatrath et al reported the following frequency of cramp: once per week (24%), several times per week (39%), once per day (18%), and several times per day (20%) and 19%

reported mild pain while majority of the patients (62%) reported severe pain, 66% of the patients had cramps during both day and night times where as 34% of the patients experienced cramps exclusively during the night.

Table 10 and figure 9 shows the various drugs that the patients took for the relief of cramp. The drugs include calcium supplements (30.76%), vitamin D (23.07%) and vitamin E (46.15%) supplements. Out of the above, Vitamin E supplements are most commonly used for the relief of cramp symptoms.

The data collected from the patients case chart shows that the most commonly prescribed diuretics are furosemide, torsemide, spironolactone and hydrochlorothiazide. Among these torsemide (31.73%) and furosemide (30.76%) are most common. Among the different diuretics prescribed in patients with muscle cramps, furosemide is the most common i.e., 42.10% of patients are using furosemide for different conditions. The daily dose of each diuretic varies in different patients depending on the severity of their clinical condition. The daily doses of each diuretic collected from the patients case chart are as follow: Furosemide (80mg, 60mg, 50mg, 40mg, 20mg, 10mg), Torsemide (40mg, 25mg, 20mg, 10mg, 5mg), Spironolactone (100mg, 50mg, 25mg), Hydrochlorothiazide (100mg). Among these drugs the frequently used diuretic in the general population and in patients with muscle cramps is Furosemide with a daily dose of 40mg (table 11 and fig 10).

Descriptive statistics such as percentage were used to characterize the study population. Association of presence of muscle cramp with selected demographic variables and clinical variables and association of CSS score with age and sodium levels were found out using  $\chi^2$  test. A P value of <0.05 was considered to be statistically significant. The P value shows that age, gender and potassium level has no association with muscle cramps i.e., age and gender does not influence muscle cramps (table 20). Table 21 shows that, sodium level is significantly associated with CSS > 9.

## CONCLUSION

Muscle cramps, notably nocturnal leg cramps, are common symptoms experienced by general medical patients, particularly the elderly. Their aetiology is varied; most commonly, these cramps are idiopathic. In this study we have evaluated the prevalence and management of diuretic induced muscle cramps in the study population. We collected patient details of 104 patients who had a history of diuretic use for at least 3 months. The study population consist of 56.73% males and remaining females. 75% of the study population comes under the age group 65-75 years. The current study highlights the association of sodium levels (hyponatremia) with muscle cramps just as in previous studies. Out of the 19 patients with muscle cramps 53.33% of the patients have hyponatremia. The



association between muscle cramps and hyponatremia was found significant ( $P$  value= 0.025) when statistical analysis was performed using Chi-Square test. The pattern of diuretic use in the study population (patients with muscle cramps) is Furosemide>Tosemide>Spironolactone>Hydrochlorthiazide with furosemide 40mg being the most commonly prescribed (30.76%).

The current study shows calcium supplements (30.76%), vitamin D (23.07%) and vitamin E (46.15%) supplements are prescribed for the relief of cramps of which vitamin E (46.15%) is the most common.

Despite a thorough and systematic evaluation in the current prospective study, we failed to show other predictors for occurrence of muscle cramps, including serum potassium level, serum calcium and magnesium levels because these measures were not available in the majority of patients. Although, vitamin E is the most commonly prescribed drug for the relief of muscle cramps, we failed to assess the effectiveness of vitamin E in treating muscle cramps.

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#### REFERENCES

1. K.D.Tripathi. Essentials of medical pharmacology. 7<sup>th</sup> Ed. 2013.chapter41,2
2. Karen Whalen, Richard Finkel, Thomas.A.Panavelil. Lippincott illustrated review s on pharmacology. 6<sup>th</sup> Ed. Chapter18, Diuretics; 241-51. Diuretics; 579\_91.
3. Kyong Chong. Diuretic Screening. Medscape database of systematic reviews [Internet] 2014[cited Apr 25, 2014]. Available from <https://emedicine.medscape.com/article/2119155-overview#a1>.
4. Gavino Casu, Pierluigi Merella. Diuretic Therapy in Heart Failure – Current Approaches. European Cardiology Review, 2015; 10(1): 42–7.
5. G. Michael Felker, Christopher M. O'Connor, Eugene Braunwald. Loop diuretics in acute decompensated heart failure. Circ Heart Fail, 2009; 2: 56-62.
6. George C.Roush, Domenic A. Sica. Diuretics for hypertension: A review and update. American Journal of Hypertension, October, 2016; 29(10): 1130-7. doi:10.1093/ajh/hpw030.
7. Shah PB, Soundararajan P, Sathiyasekaran BWC, Hegde SC. Diuretics for people with chronic kidney disease (Protocol). Cochrane Database of Systematic Reviews [internet], 2014; 10. Art. No.: CD011339. DOI: 10.1002/14651858.CD011339.
8. K P Moore, G P Aithal. Guidelines on the management of ascites in cirrhosis. Gut., 2006; 55(6): 61–72. doi: 10.1136/gut.2006.099580.
9. Domenic A. Sica. Diuretic related side effects: development and treatment. Medscape database of systematic reviews [internet], 2004. Available from [https://www.medscape.com/viewarticle/489521\\_14](https://www.medscape.com/viewarticle/489521_14).
10. Chatrath H, Liangpunsakul S, Ghabril M, Otte J, Chalasani N, Vuppalandhi R. Prevalence and Morbidity Associated with Muscle Cramps in Patients with Cirrhosis. Am J Med [Internet], 2012; 125(10): 1019–25. Available from: <http://dx.doi.org/10.1016/j.amjmed.2012.03.012>
11. Mosenkis A, Townsend RR. Muscle cramps and diuretic therapy. J Clin Hypertens (Greenwich), 2005; 7(2): 134–5.
12. Incidence of Diuretics Induced Adverse Drug Reactions in an Intensive, 2017; 8(8): 3557–62.
13. S. A, G.-C. F, A.B. L, G.-M. F, C. S, H. Z, et al. Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: A cross-sectional analysis. BMC Med [Internet], 2013; 11(1). Available from: <http://www.biomedcentral.com/1741-7015/11/83%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed11&NEWS=N&AN=2013232287>
14. Salil.k.Bhattacharya, Parantapa Sen, Arunabha Ray. Pharmacology. 2nd Ed. 2004.chapter 5, Drugs acting on the kidney, 135\_44.
15. R.S. Satoskar, Nirmala N. Rege, Raakhi.K.Tripathi, S.D. Bhandarkar. Pharmacology and pharmacotherapeutics. 25th Ed. 2017.chapter 38, diuretics and antidiuretic drugs and drug induced nephropathy, 557\_80.
16. H.P. Rang, M.M. Dale, J.M. Ritter, R.J. Flower, G.Henderson. Rang and Dale's pharmacology. 7th Ed. 2012. chapter 24, The kidney; 347\_56.
17. Joseph T.Dipiro, Robert.L, Talbert Gray c. Yee, Gary R.Matzke, Barbara G.Wells, L.michael posey. Pharmacotherapy, A pathophysiological approach. 8th Ed. Chapter 16, Cardiac arrest; 83\_98.
18. Goodman and Gillman's the pharmacological basis of therapeutics. 12th Ed. Chapter 25, Regulation of renal function and vascular volume, 671\_93.
19. Koda Kimble and Young' applied Therapeutics the clinical use of drugs. 17th Ed. Chapter19, Heart failure, 436\_56.
20. Davidson's principles and practices of medicine. 22nd Ed. Chapter 18, Heart failure, 545\_53.
21. Roger Walker, Cate Whittlesea. Clinical pharmacology and therapeutics. 5th Ed. 2007.Chapter 19, Hypertension, 295\_306.

22. Marcel Ruzicka, Brendan McCormick, Peter Magner, Tim Ramsay, Cedric Edwards, Ann Bugeja, Swapnil Hiremath. Thiazide diuretic-caused hyponatremia in the elderly hypertensive: will a bottle of Nepro a day keep hyponatremia and the doctor away? Study protocol for a proof-of-concept feasibility trial. *BioMed Central*, 2018; 4(71). doi: 10.1186/s40814-018-0263-y.
23. S. Vikas, M. Ramesh, Vanitha N. Rani, P. Thennarasu, G. Kannan. incidence of diuretics induced adverse drug reactions in an intensive cardiac care unit of a tertiary care teaching hospital. *international journal of pharmaceutical sciences and research*, 2017; 8(8): 3557-62. doi:10.13040/ijpsr.0975-8232.8(8).3557-62.
24. Louise Rabbitt Eamon C, MulkerrinShaun T. O'Keeffe. A review of nocturnal leg cramps in older people. *Age and Ageing*, 2016; 45(6): 776-82.
25. Joannes Hallegraeff, Mathieu de Greef, Wim Krijnen, Cees van der Schans. Criteria in diagnosing nocturnal leg cramps: a systematic review. *BMC*, 2017; 18(29). doi: 10.1186/s12875-017-0600-x
26. Hubert Maisonneuve, Juliette Chambe, Chloé Delacour, Joris Muller, Fabien Rougerie, Dagmar M. Haller, Michel Leveque. Prevalence of cramps in patients over the age of 60 in primary care : a cross sectional study. *BMC*, 2016; 17(111). doi.org/10.1186/s12875-016-0509-9.
27. Joan Carles Trullàs, José Luís Morales-Rull, Jesús Casado, Adriana Freitas Ramírez, Luís Manzano, Francesc Formiga. Rationale and design of the "safety and efficacy of the combination of loop with thiazide-type diuretics in patients with decompensated heart failure (CLOROTIC) trial. *Journal of cardiac failure*, 2016; 22(7): 529-36.
28. Spyridon Arampatzis, Georg-Christian Funk, Alexander Benedikt Leichtle, Georg-Martin Fiedler, Christoph Schwarz, Heinz Zimmermann, Aristomenis Konstantinos Exadaktylos, Gregor Lindner. Impact of diuretic therapy-associated electrolyte disorders present on admission to the emergency department: a cross-sectional analysis. *BMC*, 2013; 11(83). doi.org/10.1186/1741-7015-11-83.
29. Pooja Budhiraja, Rohit Budhiraja, James L. Goodwin, Richard P. Allen, Anne B. Newman, Brian B. Koo, Stuart F. Quan. Incidence of Restless Legs Syndrome and Its Correlates. *J Clin Sleep Med.*, Apr 15, 2012; 8(2): 119–24. doi: 10.5664/jcsm.1756.
30. Mary Jane Lim Fat, Seint Kokokyi, Hans Dieter Katzberg. Neurologist practice patterns in treatment of muscle cramps in Canada. *J Foot Ankle Res.*, 2013; 6(2). doi: 10.1186/1757-1146-6-2.
31. David Wile. Diuretics: a review. *Ann Clin Biochem*, 2012; 49: 419–31. DOI: 10.1258/acb.2011.011281.
32. Allen RE, Kirby KA. Nocturnal leg cramps. *Am Fam Physician [Internet]*, 2012; 86(4): 350-5. Available from <https://www.aafp.org/afp/2012/0815/p350.html>.
33. Basil N Okeahialam, Esther N Ohihoin, Jayne NA Ajuluchukwu. Diuretic drugs benefit patients with hypertension more with night-time dosing. *Ther Adv Drug Saf.*, 2012; 3(6): 273–278. doi: 10.1177/2042098612459537.
34. Fiona Blyton, Vivienne Chuter, Joshua Burns. Unknotting night-time muscle cramp: a survey of patient experience, help-seeking behaviour and perceived treatment effectiveness. *Journal of Foot and Ankle Research*, 2012; 5(7). <https://doi.org/10.1186/1757-1146-5-7>.
35. Hemant Chatrath, Suthat Liangpunsakul, Marwan Ghabril, Julie Otte, Naga Chalasani, Raj Vuppalachchi. Prevalence and Morbidity Associated with Muscle Cramps in Patients with Cirrhosis. *Am J Med.*, 2012; 125(10): 1019–1025. doi: 10.1016/j.amjmed.2012.03.012.
36. Domenic A. Sica, Barry Carter, William Cushman, Lee Hamm. Thiazide and Loop Diuretics. *J Clin Hypertens (Greenwich)*, 2011; 13: 639–643. doi.org/10.1111/j.1751-7176.2011.00512.
37. El-Hennawy AS1, Zaib S. A selected controlled trial of supplementary vitamin E for treatment of muscle cramps in hemodialysis patients. *Am J Ther.*, 2010; 17(5): 455-9. doi: 10.1097/MJT.0b013e3181b13c8f.
38. Samuel J. Mann. The Silent Epidemic of Thiazide-Induced Hyponatremia. *The Journal of Clinical Hypertension*, 2008; 10(6). doi.org/10.1111/j.1751-7176.2008.08126.x.
39. Guay DR. Are there alternatives to the use of quinine to treat nocturnal leg cramps?. *Consult Pharm.*, 2008; 23(2): 141-56. DOI: <https://doi.org/10.4140/TCP.n.2008.14>.
40. Michael Felker G. Diuretics and other therapies for hospitalized heart failure. *Indian Heart J.*, 2016; 68(1): S61–S68. doi: 10.1016/j.ihj.2015.10.386.
41. Ari Mosenkis, Raymond R. Townsend. Muscle Cramps and Diuretic Therapy. *The Journal of Clinical Hypertension*, 2007; 7(2). <https://doi.org/10.1111/j.1524-6175.2005.04094.x>
42. Wilcox CS. Metabolic and adverse effects of diuretics. *Semin Nephrol [Internet]*, 1999; 19(6): 557-68. Available from <https://www.ncbi.nlm.nih.gov/pubmed/10598543/>.
43. Barry R. Davis, Linda B. Piller, Jeffrey A. Cutler, Curt Furberg, Kay Dunn, Stanley Franklin. Role of Diuretics in the Prevention of Heart Failure. *Circulation*, 2006; 113: 2201–2210. <https://doi.org/10.61/CIRCULATIONAHA.105.544031>.
44. Steve Morgan, Kenneth L Bassett, James M Wright, Lixiang Yan. First-Line First? Trends in Thiazide Prescribing for Hypertensive Seniors. *PLoS Med.*, 2005; 2(4): e80. doi: 10.1371/journal.pmed.0020080.
45. Rachel Morgan. Water Pills & Muscle Cramps. [Internet] 2005. Available from <https://www.livestrong.com/article/446768-water-pills-muscle-cramps>.



46. Kai Ming Chow, Bonnie Ching-Ha Kwan, Cheuk Chun Szeto. Thiazide-induced hyponatremia. *J Natl Med Assoc* [Internet], Oct, 2004; 96(10): 1305–1308. Available from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2568543>.
47. Wilcox CS. Metabolic and adverse effects of diuretics. *Semin Nephrol* [Internet], 1999; 19(6): 557-68. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/10598543>.
48. Pantelis A Sarafidis, Panagiotis I Georgianos, Anastasios N Lasaridis. Diuretics in clinical practice. Part II: electrolyte and acid-base disorders complicating diuretic therapy. *Expert Opinion on Drug Safety*, 2010; 9(2): 259-273. DOI: 10.1517/14740330903499257.
49. Pantelis A Sarafidis, Panagiotis I Georgianos, Anastasios N Lasaridis. Diuretics in clinical practice. Part I: mechanisms of action, pharmacological effects and clinical indications of diuretic compounds. *Expert Opin Drug Saf.*, 2010; 9(2): 243-57. doi:10.1517/14740330903499240.
50. Juan Tamargo, Julian Segura, Luis M Ruilope. Diuretics in the treatment of hypertension. Part 1: thiazide and thiazide-like diuretics. *Expert Opin Pharmacother*, 2014; 15(4): 527-47. doi: 10.1517/14656566.2014.879118.
51. Julio D Duarte and Rhonda M Cooper-DeHoff. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert Rev Cardiovasc Ther.*, 2010; 8(6): 793–802. doi: 10.1586/erc.10.27.
52. Juan Tamargo, Julian Segura and Luis M Ruilope. Diuretics in the treatment of hypertension. Part 2: loop diuretics and potassium-sparing agents. *Expert Opin Pharmacother*, 2014; 15(5): 605-21. doi: 10.1517/14656566.2014.879117.
53. James J DiNicolantonio. Hydrochlorothiazide: is it a wise choice?. *Expert Opin Pharmacother*, 2012; 13(6): 807-14. doi: 10.1517/14656566.2012.67
54. DeRubertis FR, Michelis MF, Beck N, Davis BB. Complications of diuretic therapy: severe alkalosis and syndrome resembling inappropriate secretion of antidiuretic hormone. *Metabolism clinical and experimental*. [Internet], 1970; 19(9): 709-19. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/5460000>
55. Fichman MP, Vorherr H, Kleeman CR, Telfer N. Diuretic-induced hyponatremia. *Ann Intern Med.*, 1971; 75(6): 853-863. DOI: 10.7326/0003-4819-75-6-853
56. Jennifer Barber, Tricia M McKeever, Sarah E McDowell, Jennifer A Clayton, Robin E Ferner, Richard D Gordon, Michael Stowasser et al. A systematic review and meta-analysis of thiazide-induced hyponatraemia: time to reconsider electrolyte monitoring regimens after thiazide initiation?. *Br J Clin Pharmacol*, 2015; 79(4): 566–577. doi: 10.1111/bcp.12499
57. Sullivan RC, Freemon FR, Caranasos GJ. Complications from diuretic therapy with ethacrynic acid and furosemide. *South Med J* [Internet], 1971; 64(7): 869-72. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/5090186/>.
58. Kim KE, Onesti G, Moyer JH, Swartz C. Ethacrynic acid and furosemide. Diuretic and hemodynamic effects and clinical uses. *Am J Cardiol*, 1971; 27(4): 407-15. [https://doi.org/10.1016/0002-9149\(71\)90438-3](https://doi.org/10.1016/0002-9149(71)90438-3).
59. Olesen KH. Intravascular, interstitial and intracellular phase changes during acute furosemide or ethacrynic acid diuresis. *Isr J Med Sci* [Internet], 1969; 5(4): 942-6. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/5820551/>.
60. Martinez-Maldonado M. Electrolyte disturbances resulting from diuretic therapy. *Tex Med* [Internet], 1973; 69(7): 83-7. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/4720638/>.
61. Perez-Stable EC, Materson BJ. Diuretic drug therapy of edema. *Med Clin North Am* [Internet], 1971; 55(2): 359-72. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/4926056/>.
62. Reubi FC. Combination diuretic drug therapy. *Cardiovasc Clin* [Internet], 1971; 2(3): 197-210. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/4950425/>.
63. Leiter L. Combinations of diuretics in the treatment of edema. *Am Heart J* [Internet], 1970; 80(3): 422-6. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/4915356/>.
64. Carlier J, Rorive G, Bovy P. Diuretics in cardiac insufficiency. *Acta Clin Belg* [Internet], 1977; 32(3): 198-208. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/602609/>.
65. Reubi FC. Combination diuretic drug therapy. *Cardiovasc Clin*, 1971; 2(3): 197-210. <https://doi.org/10.2165/00003495-199855020-00001>
66. Hall WD. Clinical use of diuretics in congestive heart failure. *Med Times*, 1979; 107(1): 24-32. doi: 10.1155/2015/975934
67. Muller J. Spironolactone in the management of congestive cardiac failure: a review. *Clin Ther* [Internet], 1986; 9(1): 63-76. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/2880664/>
68. Prichard BN1, Owens CW, Woolf AS. Adverse reactions to diuretics. *Eur Heart J* [Internet], 1992; 13: 96-103. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/1486914/>
69. Wilcox CS. Metabolic and adverse effects of diuretics. *Semin Nephrol* [Internet]. Nov, 1999; 19(6): 557-68.
70. Wilcox CS. Metabolic and adverse effects of diuretics. *Semin Nephrol* [Internet], Nov., 1999; 19(6): 557-68. Available from <https://www.ncbi.nlm.nih.gov/m/pubmed/10598543/>.
70. Reyes AJ. Pharmacologic bases of cardiovascular therapy with diuretics. *Arch Inst Cardiol Mex* [Internet], 1981; 51(3): 291-303. Available from <https://www.ncbi.nlm.nih.gov/pubmed/7283541>.

71. Kyu Sig Hwang, Kyu Sig Hwang, Thiazide-Induced Hyponatremia. *Electrolyte and Blood Pressure*, 2010; 8(1): 51–57. doi: 10.5049/EBP.2010.8.1.51.