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RESEARCH ARTICLE

TO EVALUATE THE EFFICACY AND SAFETY OF VITAMIN D_3 AS AN ADD ON THERAPY TO DICLOFENAC FOR TREATMENT OF MASTALGIA: A RANDOMISED CONTROLLED TRIAL

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Abstract

Background: Mastalgia is a medical term used for breast pain. Approximately 66% to 80% of women experience some type of breast pain at least sometime in their lives, and in 10 to 20% of the cases, it is severe.

Objective: This study aimed to evaluate the efficacy of vitamin D_3 as an add on therapy to diclofenac for decreasing the breast pain of mastalgia patients attending the surgery OPD of a rural tertiary care hospital in Haryana.

Material and Methods: A total of 123 treatment naive female patients of age group 15-45 years who presented with mastalgia ≥ 5 days in the prior month and with pain intensity ≥ 3 on VAS scale were enrolled in the study based on inclusion and exclusion criteria. Patients were divided into three groups- group A, B and C based on serum vitamin D levels.VitaminD insufficient patients were randomly divided into Group A and Group B. Vitamin D sufficient patients were put in Group C. All the patients were given Tab. Diclofenac 100 mg SR SOS for 12 weeks.Patients in group A were additionally supplemented with Vitamin $D_3$60,000 IU once a week for 8 weeks. Patients were evaluated for breast pain at baseline and at 3, 6, 9 and 12 weeks by breast pain questionnaire (BPQ). Serum vitamin D levels were done at baseline and 12 weeks.

Results: Maximum reduction in the severity of pain was observed in group A.Highly significantcorrelation was found between vitamin D insufficiency and severity of mastalgia.

Conclusion: Vitamin D as an add on therapy to diclofenac has a significant role in improvement of mastalgia.

Introduction:-

Mastalgia or breast pain is one of the leading complaints among women aged 30–50 years. During their lifetimes, 70% of women need to consult a physician due to breast pain.[1]Sometimes it may be severe enough to affect physical, social, mental and sexual lives of the women.Mastalgia can be classified into cyclical mastalgia, non-cyclical mastalgia and extramammary pain.

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Cyclical breast pain is associated with the menstrual cycle, with an onset around the late luteal phase and cessation or reduction around the menstrual phase. The pain is typically bilateral in nature and commonly seen in premenopausal women in the third or fourth decades of life.[2]The various aetiologies have been proposed for cyclic mastalgia which include hormonal changes, inflammatory processes and psychological disturbances.[3]Non-cyclical breast pain has no proven relationship with the menstrual cycle and is most commonly seen in the elderly patient group. The onset is typically around the fourth and fifth decade. Non-cyclicalbreast-pain is more likely to have an anatomical rather than hormonal cause.[4]Extramammary mastalgia refers to the breast pain that is originating from a location outside the breast, such as the heart, lung, chest wall, or the oesophagus. Extramammary breast pain feels as if it starts in the breast tissue, but in fact, it is a referred pain having its origin somewhere else. For example, pain originating from the chest wall (costochondritis), epigastric pain in GERD can be referred to give a false impression of breast pain.[5]

The treatment options for mastalgia are classified into non-pharmacological and pharmacological modalities. Non-pharmacological recommendations include education, relaxation training, and wearing a well fitted bra. Pharmacological interventions involve hormonal (Danazol, bromocriptine, tamoxifen, gestrinoneetc) and nonhormonal therapies (dietary modification, NSAIDS, evening primrose oil).[6,7]

Vitamin D has been shown to play an important role in the development and function of the mammary gland. Vitamin D deficiency is associated with increased levels of oestrogen & progesterone which cause ductal dilatation and is responsible for breast pain prior to the onset of menstruation.[8]This could be the underlying mechanism by which vitamin D deficiency results in breast tissue tenderness.With increase in vitamin D levels, a reduction in progesterone and oestrogen has been seen.[9] In our opinion, current knowledge about the association between vitamin D deficiency and mastalgia is meagre. Hence this study is being planned to assess the effect of vitamin D supplementation on symptoms of mastalgia.

Materials and Methods:-

This was a prospective, open-label, randomized, comparative clinical study. The study was started after getting approval from the institutional ethical committee. The duration of the study was one year starting from the date of approval of the protocol.

Treatment naive female patients of age group 15-45 years who presented with mastalgia ≥ 5 days in the prior month, pain intensity ≥ 3 on VAS scale were enrolled in the study. A written informed consent was obtained from all the patients. Patients with known or suspected breast cancer, BIRADS score >3, severe deficiency of vitamin D (<10ng/ml) were excluded from the study. All patients had undergone triple assessment after history i.e. clinical examination, imaging (USG/mammography) and FNAC (if needed) to rule out breast cancer. The eligible patients were divided into three study groups i.e. Group A, Group B, and Group C on the basis of serum vitamin D levels at the baseline. Patients with insufficient vitamin D levels (10-30 ng/ml) were randomly divided into Group A and Group B. Vitamin D sufficient (30-60ng/dl) patients were put in Group C. Each group had 41 patients. In group A, patientsreceived Vitamin $D_3$60,000 IU once a week for 8 weeks + Tab. Diclofenac 100 mg SR SOS for 12 weeks. In group B and C, patientsreceived only Tab. Diclofenac 100 mg SR SOS for 12 weeks.

Breast pain in the patients were assessed by breast pain questionnaire (BPQ)at the baseline and at the time of follow up on 3, 6, 9 and 12 weeks. BPQ is a modified form of SF-MPQ (short form of Mc-Gill pain questionnaire).[10-13]

Each patient's pain was assessed at the baseline as being either cyclical or non-cyclical.Sensorycomponent of breast pain was assessed based on 11 descriptors (throbbing, shooting, stabbing, sharp, cramping, gnawing, burning, aching, heavy, tender, splitting) and affective component of pain was assessed based on 4 descriptors(tiring, sickening, fearful and punishing). Each dimension was given score from 0-3, where 0 meant no pain, 1 means mild pain, 2 means moderate pain and 3 means severe pain. Total maximum possible score was 33 and 12 for sensory and affective component respectively.% Sensory component score was calculated by the sum of scores of each sensory descriptor divided by 33 and expressed as a percentage value.% Affective component score was calculated by the sum of scores of affective descriptors as a percentage of maximal affective score of 12. % Q total score was calculated by sum of sensory and affective component scores and divided by 45, expressed as percentage value.

Mastalgia pain intensity in the patients was scored from 0-10 on a visual analogue scale (VAS). No pain was given a score of 0, whereas 10 was the worst imaginable pain. % VAS was calculated by dividing VAS score by 10 and expressed as a percentage value.

Mc-Gill present pain index (PPI) was calculated based on the classification where no pain, mild pain, discomforting, distressing, horrible and excruciating pain was given a score of 0, 1, 2, 3, 4 and 5 respectively.% PPI was calculated by score of PPI divided by 5 and expressed as a percentage value.Chronicity score of mastalgia was estimated based on criteria in whichcontinuous, steady & constant pain was given a score of 1; rhythmic, periodic & intermittent pain was given a score of 2 whereas brief, momentary & transient pain was given a score of 3.Size of painful area in percentage was estimated in each patient using breast drawings.[11]Quality of life (QOL) score of each patient was calculated based on 4 parameters (sexual activity, physical activity, work and sleep) on a scale of 0-3,where 0 means no effect & 1, 2, 3 signify mild, moderate, and severe effect on the assessed parameters. %QOL was calculated as sum of score of QOL parameters as a percentage of maximal QOL score of 12.

% Total breast pain score was calculated for each patient at each follow up by adding % Q total, %PPI, %VAS and %QOL. Severity of breast pain for each individual was calculated at all the follow up visits based on total breast pain score. Total breast pain scores from 0-100, 100-200 and >200wasconsidered as mild, moderate and severe pain respectively.Each patient's serum vitamin D level was calculated at the baseline and at the end 12th week.Number of times analgesics were required in past 3 weeks was calculated in each patient at all the follow ups.

Since vitamin D supplementation was done only in group A, the severity of mastalgia was analyzed before & after vitamin D supplementation only in group A patients. For the purpose of correlation, patients were categorized into those having mild-moderate mastalgia (0-200 TBP) and severe mastalgia (200-400 TBP).

Safety assessment was also carried out at all the follow ups after initiation of the respective therapy in all three groups.

Results:-

A total of 123 female patients participated in the study. The mean age of the patients in all the three groups were comparable- 29.80±1.17 years in Group A, 30.76±1.04 years in Group B, 31.80±0.84 years in group C. Group wise distribution of cyclical and non-cyclical pain at the baseline is shown in table 1.

% Sensory component, % affective component and % Q total values are shown in table 2. % VAS, % PPI, % QOL and % TBP values are shown in table 3.

Chronicity score of mastalgia

At the baseline, in all the groups most common chronicity score was found to be 2 which represents rhythmic, periodic and intermittent type of pain.During the study period, patients reported that their pain shifted from continuous type to intermittent or transient type of pain. Maximum shift was observed in group A. On intergroup comparison, highly significant difference was observed between group A and B and group A and C at the end of 12th week only.

Size of painful areas

The size of painful area was reduced progressively at every follow up in all three groups butsignificant difference between the groups was observed after 6th week and highly significant difference was observed after 9th week. By the end of the study lowest painful area size was observed in group A and highest painful area size was observed in group B as shown in figure 1.

Site of pain

On evaluating the data about site of pain, it was found that bilateral mastalgia is more common than unilateral among the study population.Over the study period number of patients having bilateral pain had reduced in the study population.

Severity of breast pain

The percentage of patients having mild, moderate and severe pain according to the total breast pain scores is shown in table 4. Severity of mastalgia reduced over the study period and by the end of the studyit was found that only

9.8% patients in group B was left with severe breast pain. A and C group patients did not report severe breast pain at the end of the study.

Analgesic requirement
Analgesic requirement reduced progressively over the study period. By the end of study, maximum analgesic requirement was observed in group B and minimum analgesic requirement was observed in group A as shown in figure 2.

Serum vitamin D levels
Mean serum vitamin D levels at the baseline were 17.37±0.55, 15.83±0.68 and 35.17±0.57 ng/ml in group A, B and C respectively. At the end of 12 weeks, mean serum vitamin D levels were found to be 31.41±0.46, 15.95±0.66 and 33.43±0.60 in group A, B and C respectively.On intragroup comparison,highly significant increase in the value of vitamin D was observed only in group A.

Correlation between vitamin D insufficiency and mastalgia
Correlation between vitamin D insufficiency and mastalgia was evaluated as shown in table 5. Highly significant correlation was found between vitamin D insufficiency and severity of mastalgia. Patients exhibiting insufficient levels of vitamin D had higher severity of breast pain. Notably, subsequent supplementation with vitamin D led to a statistically significant reduction in the severity of the pain experienced by these patients.

Safety assessment
Safety assessment was carried out in all the patients. Pain abdomen and nausea were the most frequent complaints given by the patients. There were no serious side effects noted.

Discussion:-

In our study, most common sensory descriptorsobservedamong the study population were tender, burning, heavy and aching.Most common affective descriptor observed was sickening followed by tiring andmost common type of PPI reported by the patients was discomforting (Score-2). Transition from continuous to intermittent type of pain was observed in majority of patients.Similar findings were shown in the study conducted in Chicago, IL, USA by Khan SA, et al who studied the characteristics of cyclical and non-cyclical mastalgia using a modified McGill pain questionnaire.[11]

In our study, it was observed that % VAS score reduced progressively in all the groups. The highest score was observed in group B at all the follow up visits.Our findings were corroborated by another study which was conducted by Sen M, et al at Turgut Ozal University, Turkey to determine the coexistence of mastalgia and fibromyalgia.[12]

Qualityof life (QOL) scores of our study indicate a direct correlation between mastalgia and QOL. After intervention, each group had progressive and statistically significant reduction in score and group Ahad maximum reduction in scores. Most common parameter affected in patients was sleep.A study which was conducted by Carmichael AR, et al in UK observed that breast pain affected the components of QOL such as sleep in 43% of women, sex life in 30% of women and work in 28% of women.[13]

All the participants of our study underwent serum vitamin D level estimation at baseline and end of 12 weeks. There was no statistically significant difference in vitamin D levels in group B & C. However, there was an average increase in serum vitamin D levels of 10.95 ng/mlin group A patients that can be attributed to Vitamin D_3 supplementation throughout the study duration. Similar finding was observed in a prospective study was conducted by Thakur N, et al in 2020 at SKIMS Soura, Srinagar, J&K to study the association between Vit D deficiency and mastalgia among patients visiting outpatient department. All patients with low vitamin D were given vitamin D supplementation. Mean serum vitamin D level at the recruitment was 10.86 ng/ml and after vitamin D supplementation was 27.59 ng/ml.[14,15]

The %TBP score also showed progressive decrease at each follow-up visit. At baseline, group B had highest score. In all the groups number of patients suffering from severe breast pain also decreased with group A showing highest reduction and Group B showing least reduction. It indicates that vitamin D_3 supplementation produces relief in mastalgia. A study which was conducted by Carmichael AR, et al in UK to evaluate mastalgia in patients reported

that median of total breast pain was 137. Based on total breast pain score, mastalgia was graded as mild (score 0-100) in 26%, moderate (score 101-200) in 59% and severe (score >200) in 15% of patients.[13]This study however did not study the effect of vitamin D supplementation on mastalgia severity.Breast pain is thought to be related to inflammation in the breast tissue or the muscles around the breastand increased sensitivity of the pathways that transmit pain signals.[16]Vitamin D has the ability to reduce inflammation in the bodyby controlling the immune cells, blocking substances that cause inflammation.

Our study showed highly significant correlation between vitamin D insufficiency and severity of mastalgia. Patients with insufficient vitamin D levels had more severe breast pain whereas patients with sufficient vitamin D levels had less severe breast pain.A study was conducted by Sarkar DK, et al at IPGMER, Kolkata, India to evaluate the role of vitamin D in relieving mastalgia.The patients were randomly divided into 2 groups: one received evening primrose oil (EPO) only and the other group received EPO and vitamin D at a dose of 60,000 units per week over a period of 6-12 weeks. The authors concluded that supplementation of vitamin D in mastalgia is strongly associated with reduction of breast pain.[9,17]Thus this study substantiates the findings of our study.

Summary and Conclusion:-

The present study concluded that vitamin D_3 as an add on therapy with diclofenac decreases the sensory component score, affective component score, pain intensity score, Mc-Gill present pain index (PPI) of mastalgia more effectively as compared to diclofenac alone.Vitamin D_3 when given with diclofenac resulted in shift of a greater number of patients from continuous to intermittent and bilateral to unilateral type of pain than diclofenac alone. It is also more effective in improving the quality of life and reducing the size of painful area in patients with mastalgia.Total severity of breast pain reduced more effectively when vitamin D_3 was added with diclofenac. Highly significant correlation was found between vitamin D insufficiency and severity of mastalgia.

Thus, addition of vitamin D_3todiclofenac seems to be a better treatment of mastalgia as compared to diclofenac alone, although more studies are required to confirm these findings.

Table 1:- Number of patients having cyclical or non-cyclical pain.

Group	Cyclical mastalgia	Non-cyclical mastalgia
Group A (n=41)	26	15
Group B (n=41)	21	20
Group C (n=41)	24	17

Table 2:- Mean % sensory, % affective and % Q total score of mastalgia.

Parameter	Group	0 week (Mean ± SEM)	End of 3 weeks (Mean ± SEM)	End of 6 weeks (Mean ± SEM)	End of 9 weeks (Mean ± SEM)	End of 12 weeks (Mean ± SEM)
% sensory component score	**A**	31.26±1.27	23.35±1.07$^{\#\#}$	15.74±1.21$^{\#\#}$	8.13±1.20$^{\#\#}$	6.50±1.11$^{\#\#}$
	B	32.22±1.39	26.68±1.64$^{\#\#}$	24.68±1.82$^{\#\#}$	20.19±1.90$^{\#\#}$	19.80±1.92$^{\#\#}$
	C	28.30±1.18	22.17±1.18$^{\#\#}$	16.18±1.34$^{\#\#}$	12.93±1.44$^{\#\#}$	11.01±1.29$^{\#\#}$
	p value	0.086	0.047*	0.001**	0.001**	0.001**
% affective component score	**A**	40.24±1.39	29.87±1.81$^{\#\#}$	17.88±1.68$^{\#\#}$	8.53±1.80$^{\#\#}$	2.80±0.62$^{\#\#}$
	B	38.00±2.41	36.38±2.66$^{\#}$	33.53±2.97$^{\#\#}$	32.72±3.33$^{\#\#}$	11.52±1.27$^{\#\#}$
	C	35.16±1.65	27.03±1.66$^{\#\#}$	18.90±1.99$^{\#\#}$	14.63±2.30$^{\#\#}$	4.06±0.70$^{\#\#}$
	p value	0.162	0.007*	0.001**	0.001**	0.001**
% Q total score	**A**	36.02±1.31	26.88±1.29$^{\#\#}$	17.47±1.35$^{\#\#}$	8.82±1.39$^{\#\#}$	7.31±1.33$^{\#\#}$
	B	36.17±1.63	31.35±1.91$^{\#\#}$	28.97±2.16$^{\#\#}$	25.78±2.32$^{\#\#}$	24.62±2.39$^{\#\#}$
	C	27.64±1.40	23.05±1.47$^{\#\#}$	17.47±1.66$^{\#\#}$	14.34±1.73$^{\#\#}$	11.84±1.50$^{\#\#}$
	p value	0.097	0.015*	0.001**	0.001**	0.001**

- *Indicates significant difference between the groups. ($p \leq 0.05$)
- ** Indicates highly significant difference between the groups. ($p \leq 0.001$)
- # Indicates significant difference as compared to the baseline value. ($p \leq 0.05$)

- ## Indicates highly significant difference as compared to the baseline value. ($p \leq 0.001$)

Table 3:-Mean % VAS, % PPI, %QOL and % Total breast pain score.

Parameter	Group	0 week (Mean ± SEM)	End of 3 weeks (Mean ± SEM)	End of 6 weeks (Mean ± SEM)	End of 9 weeks (Mean ± SEM)	End of 12 weeks (Mean ± SEM)
% VAS	**A**	50.00±1.56	37.56±1.47##	18.54±1.80##	9.76±1.92##	7.56±1.73##
	B	50.98±1.43	43.41±2.17##	39.51±2.79##	36.10±3.36##	35.12±3.37##
	C	47.32±1.21	33.41±1.58##	23.90±2.23##	17.80±2.62##	14.39±2.41##
	p value	0.168	0.001*	0.001*	0.001*	0.001*
% PPI	**A**	52.20±2.08	43.90±1.43##	32.20±2.19##	20.0±2.41##	12.68±2.68##
	B	50.24±1.86	47.80±1.96	41.95±2.40##	36.59±3.48##	36.10±3.43##
	C	48.78±1.56	41.46±1.89##	30.73±2.21##	23.90±2.81##	16.59±2.41##
	p value	0.427	0.043*	0.001**	0.001**	0.001**
% QOL	**A**	44.91±1.48	31.70±2.04##	17.88±1.63##	7.72±1.98##	6.91±1.86##
	B	40.44±2.04	36.78±2.61#	33.53±2.98##	30.08±3.37##	29.26±3.17##
	C	42.68±1.59	31.70±1.95##	19.10±1.62##	8.73±1.97##	7.92±1.86##
	p value	0.19	0.18	0.001**	0.001**	0.001**
% TBP	**A**	188.54±5.45	140.78±5.03##	86.09±6.30##	46.30±7.27##	34.47±7.23##
	B	177.84±6.02	159.36±7.41##	143.97±9.51##	128.54±11.93##	125.11±11.80##
	C	150.08±5.32	118.66±6.19##	87.92±7.31##	66.41±8.60##	50.74±7.55##
	p value	0.249	0.004*	0.001**	0.001**	0.001**

- *Indicates significant difference between the groups. ($p \leq 0.05$)
- ** Indicates highly significant difference between the groups. ($p \leq 0.001$)
- # Indicates significant difference as compared to the baseline value. ($p \leq 0.05$)
- ## Indicates highly significant difference as compared to the baseline value. ($p \leq 0.001$)

Table 4:- Severity of breast pain.

Group	0 week			End of 12 weeks		
	Mild	**Mod.**	**Sev.**	**Mild**	**Mod.**	**Sev.**
A (%)	0	58.5	41.5	90.2	9.8	0
B (%)	0	70.7	29.3	26.8	63.4	9.8
C (%)	0	87.8	12.2	92.7	7.3	0

Table 5:- Correlation between vitamin D insufficiency and mastalgia.

Vitamin D supplementation	% Severity of mastalgia	
	% of patients with mild-moderate mastalgia (0-200 TBP)	**% of patients with severe mastalgia (200-400 TBP)**
At baseline (Before supplementing vitamin D)	58.5%	41.5%
At the end of study (After completion of vitamin D supplementation)	100%	0

Figure 1:- Mean size of painful area (in %).

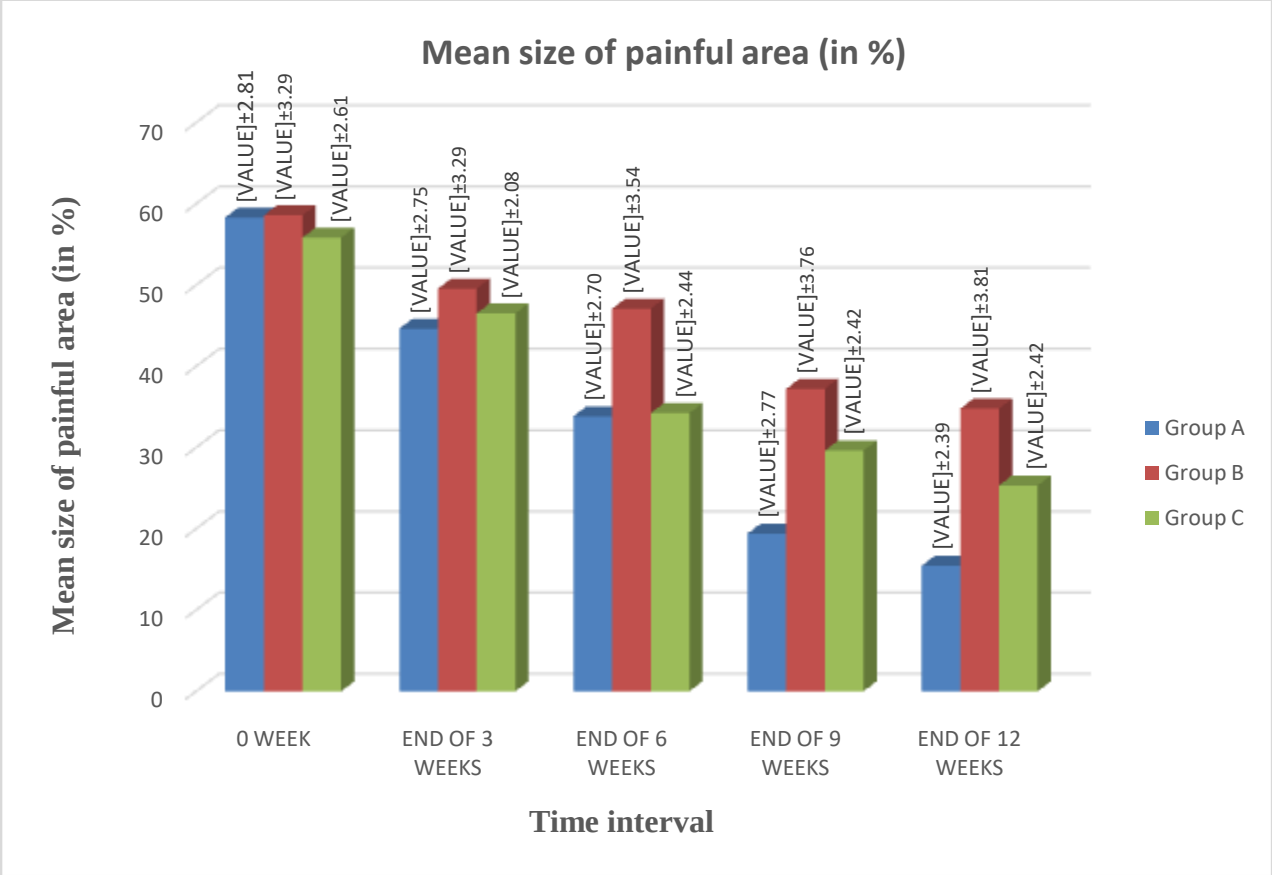
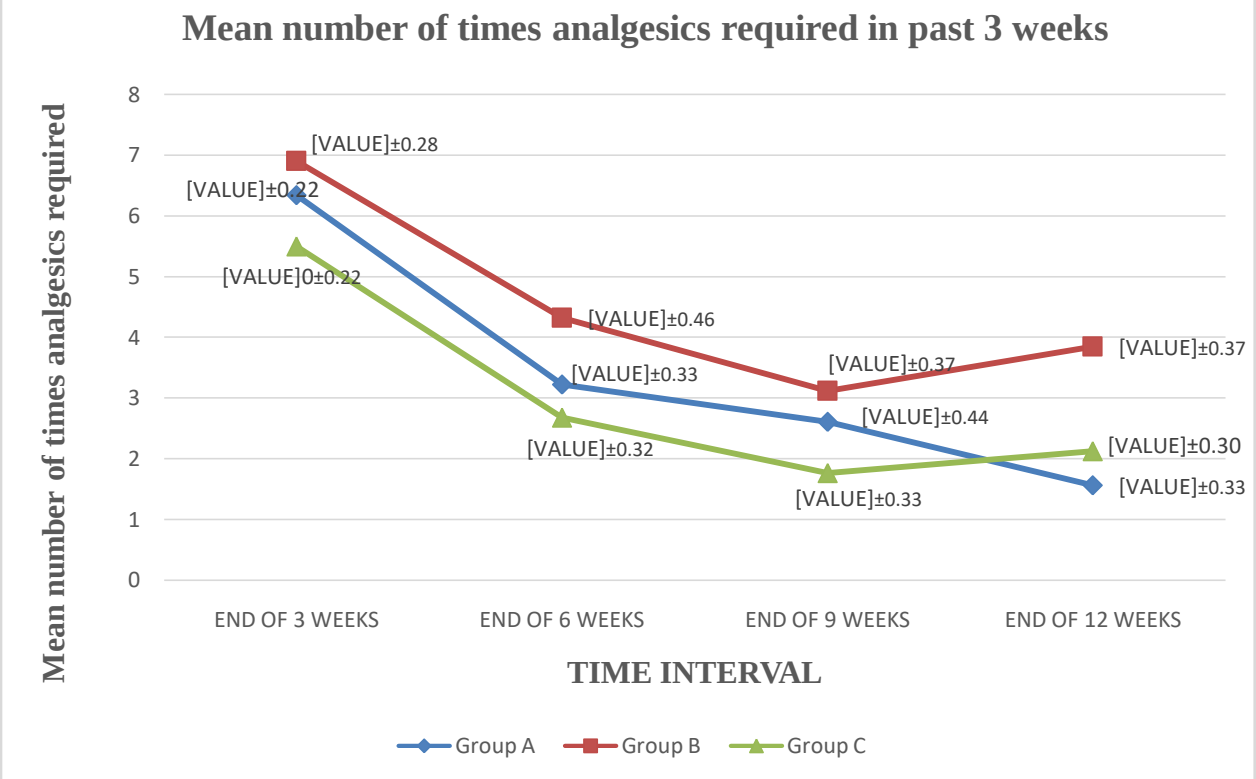


Figure 2:-Mean number of times analgesics required in past 3 weeks.



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