Preemptive analgesia for primary dysmenorrhea : A randomized controlled clinical trial

Original Article

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ABSTRACT

Background: Spasmodic dysmenorrhea is one of the commonest painful attacks that affects young ladies. Non steroidal anti-inflammatory (NSAID) drugs are considered as one of the main treatment options. Different pain management modalities concern with pretreatment with analgesia before the painful stimuli that defined as preemptive analgesia.

Aim: This study aimed to evaluate the possible effect of administration of NSAIDs before the onset of pain in the anticipating menstrual cycle.

Materials and Methods: One hundered young ladies ranged from 15-25 years old were randomly divided into two groups. Group 1 received mefinamic acid 2 days before the anticipating date of menstruation and continued throughout the first 2 days of menstruation and group 2 received the same medication however started with the onset of symptoms only.

Results: Both groups were comparable regarding age, education and menstrual characters. The average pain score was nearly the same in both groups (8.78 ± 1.07 and 8.66 ± 1.04) and it was significantly decrease after intervention in both groups. The decrease in pain score was more in the girls treated before menstruation (4.24 ± 1.57) compared to (7.20 ± 1.77) in the girls treated after onset of menstruation and the difference was statistically significant. The percentage decrease in pain score among the girls of premenstrual treatment ranged from 14.28% to 80.0% with median decrease 55.56%, compared to 0.0% to 62.5% with median decrease 10.56% in the group treated at onset of menstruation. The difference was also statistically significant (*P <0.001*).

Conclusion: NSAIDS can be used effectively to prevent and control primary dysmenorrhea associated symtoms if used before the appearance of symptoms, and targeted groups are in great chance to practice an easier life throughout the entire menstrual cycle.

Key Words: Awareness, barriers, educated young Egyptians, sexual and reproductive health problems

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INTRODUCTION

Primary dysmenorrhea, or painful menstruation in the absence of pelvic pathology, is a common, and often debilitating, gynecological condition that affects between 45 and 95% of menstruating the girls. Despite the high prevalence, dysmenorrhea and its occasionally marvelous impact on quality of life as illustrated by many large worldwide different studies[1], it is often poorly treated, and even disregarded, by health professionals, pain researchers, and the the girls themselves, who may accept it as a normal part of the menstrual cycle[2].

The most widely accepted explanation for the pathogenesis of primary dysmenorrhea is the overproduction of uterine PGs. Enhanced release of PGs derived from arachidonic acid, from disintegrating cells during endometrial sloughing, is believed to cause myometrial hyper -contractility, resulting in ischemia and hypoxia of the utersine muscle, and, ultimately, hyper-sensitization of pain nerve fibers resulting in pain[3].

Repeated monthly painful episodes may lead to the development of central sensitivity to pain[4] where abnormal expansion of pain by mechanisms within the central nervous system (CNS), and therefore a greatly enhancement response to normal peripheral sttimuli[5, 6]. This intensified excitability of nociceptive neurons not only increases their sensitivity to inputs from afferents from damaged or inflamed sites, but also to other convergent inputs[7].

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Non-steroidal anti-inflammatory drugs (NSAID) are a group of the commonest used medications for pain control in primary dysmenorrhea, act by inhibiting the enzyme that catalyzes the conversion of arachidonic acid to cyclo-oxygenase (COX) which in turn inhibits the production of PGs. Since suppression of PG formation results in a reduction in uterine PG secretion with further less vigorous uterine contractions[8, 9].

The idea of pain prevention was first introduced into clinical practice by Crile in 1913 and further developed by Wall and Woolf who suggested that simple changes in the timing of treatment can have intense effects on pain[10, 11]. The concept of preemptive analgesia to reduce the magnitude and duration of postoperative pain was paved in 1983 by Woolf[12] who showed evidence for a central component of post injury pain hypersensitivity in experimental studies. The timing of analgesic treatment in relation to the noxious (surgical) injury was one of the most important issues. Subsequently, an overwhelming amount of experimental data demonstrated that various anti-nociceptive techniques applied before pain stimuli were more effective in reducing the post injury central sensitization phenomena as compared with administration after injury[13].

To our knowledge, there isn't any study that adopt this idea in pain prevention as a method for management of primary dysmenorrhea.

AIM OF THE WORK

The aim of this study is to evaluate the possible effect of administration of NSAIDs before the onset of pain in the anticipating menstrual cycle guided by the concept of preemptive analgesia.

PATIENTS AND METHODS

After obtaining the approval of Mansoura Faculty of Medicine Institution Research Board (MFM_IRB), and after registration of this work on clinical trial.gov , this prospective randomized, parallel group study was conducted at Mansoura University Hospital, Egypt.

Ladies from 15-25 years old who are nulliparous, non-married with regular menstrual cycles and diagnosed to have primary dysmenorrhea after exclusion of any organic pelvic causes and able to swallow tablets were eligible for this study. The severity of primary dysmenorrhea will be matched for each patient with the visual pain analogue that scored from 1-10. The exclusion criteria included ladies with irregular cycles or with any associated local causes (pelvic infection, endometriosis, fibroid or others), patients with familial Mediterranean fever or other inter-menstrual attacks of abdominal pain, patients with gastric or duodenal ulcers or gastritis or other contraindications to non steroidal anti-inflammatory drugs., patients receiving any hormonal treatment and those with any bleeding tendencies or known to have hypersensitivity to Mefenamic acid were also excluded.

The study was conducted in two phases, each measuring two menstrual cycles; pre-intervention two menstrual cycles before the intervention and post-intervention two menstrual cycles after the intervention

All the participants were given a written consent before enrollment in the study. All patients participating in the study were randomly allocated into two groups; premenstrual treatment group 1 and menstrual treatment group 2.

The girls in group 1 received a preemptive analgesia in the form of Mefenamic acid (NSAIDs) 500 mg tablet every 8 hours on a full stomach starting 2 days before the anticipating date of menstruation. Patients in this group received the medication before they feel the dysmenorrhic spasmodic pain and continued throughout the first 2 days of menstruation. The girls allocated in group 2 received the medication (Mefenamic acid) 500 mg tablet every 8 hours on a full stomach only after the onset of pain.

The randomization was simple and balanced (1:1) and was carried out by a nurse through sealed, unlabeled opaque envelopes containing computer- generated random numbers. The participants, caregivers and investigators were not blind to group assignment.

The amplitude of dysmenorrhic pain was given a score according to the Visual pain analogue scale[14] daily before bedtime. The pre-intervention and post-intervention score of pain was measured in each group.

The sample size was calculated using the computer statistical software G*Power 3.1.9.2 9 Fisher's exact test, two tailed significance, alpha error probability=0.05, power= 90%, allocation ratio for groups=1. The estimation of the sample size was based on the previously reported analgesic effect of 60% with treatment starting with the onset of pain[15] and the preemptive 90% relief of pain if used before the pain signals started the pain pathway[16]. For detection of a difference 30% between the studied groups, a sample size of at least 84 the girls (42 in each group), 50 patients will be investigated in each group.

STATISTICAL ANALYSIS:

The statistical analysis was performed using the IBM SPSS Statistics, version 20.0 for windows. Continuous variables were expressed as mean ±standered deviation (SD) and categorical variables were expressed as

frequencies and percentages. The normality distributions of continuous variables were tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Differences among continuous variables with normal distribution were compared with the t-test. While for continuous variables without normal distribution, non-parametric tests were used and differences were compared with the Mann-Whitney U-test. Differences between percentages were compared with the Chi square (X^2) test. *P value ≤0.05* was considered statistically significant.

RESULTS

The age of the girls in both groups ranged from 15-25 years, with average 18.78 ± 2.14 and 18.46 ± 2.11 years in premenstrual and menstrual groups, respectively, with no significant difference. Nearly, two third in each group were from urban areas and about a half had secondary education.

The age of menarche in both groups ranged from 11-15 years, with average 12.48 ± 0.97 and 12.64 ± 0.92 years in premenstrual and menstrual groups, respectively, with no significant difference. Both groups were matched as regard their characteristics (Table 1).

The average pain score was nearly the same in both groups (8.78 ± 1.07 and 8.66 ± 1.04), and it was significantly decrease after intervention in both groups. The decrease in pain score was more in the girls treated before menstruation (4.24 ± 1.57) compared to (7.20 ± 1.77) in the girls treated after onset of menstruation and the difference was statistically significant (Table 2).

The range of decreasing in pain score ranged from 1.0 to 8.0 in premenstrual group with median 5.0 degrees, while it decrease in the other group ranged from 0.0 to 5.0 with median 1.0 degree, the difference was statistically significant (Table 3).

The percentage decrease in pain score among the girls of premenstrual treatment ranged from 14.28% to 80.0% with median decrease 55.56%, compared to 0.0% to 62.5% with median decrease 10.56% in the group treated at onset of menstruation. The difference was also statistically significant (*P <0.001*) (Tables 4 and 6)

The length of the cycle was not changed, while duration of menstrual flow became significantly shorter in the group of premenstrual treatment and the severity of the amount of menstrual flow became less after treatment with no significant difference (Table 5).

The percentage decrease in pain score among the girls of premenstrual treatment ranged from 14.28% to 80.0% with median decrease 55.56%, compared to 0.0% to 62.5% with median decrease 10.56% in the group treated at onset of menstruation. The difference was also statistically significant (*P <0.001*).

Table 1: Characteristics of the studied girls

Characters	Items	Studied Groups				Significance test
		Pre-Menstrual		Menstrual		
		No	%	No	%	
Age (years)	15-	17	34.0	18	36.0	$X^2 = 0.714$, P 0.677
	18-	20	40.0	24	48.0	
	21-25	13	26.0	8	16.0	
	Mean ± SD	18.78 ± 2.14		18.46 ± 2.11		t=0.753,P0.454
Residence	Rural	17	34.0	19	38.0	$X^2 = 1.581$, P 0.453
	Urban	33	66.0	31	62.0	
Education	Primary	13	26.0	15	30.0	$X^2 = 1.875$, P 0.392
	Secondary	21	42.0	25	50.0	
	High	16	32.0	10	20.0	
Age at menarche (years)	11	5	10.0	3	6.0	$X^2 = 2.119$, P 0.730
	12	26	52.0	22	44.0	
	13	11	22.0	17	34.0	
	14	6	12.0	6	12.0	
	15	2	4.0	2	4.0	
	Mean ± SD	12.48 ± 0.97		12.64 ± 0.92		t=0.844,P0.401

Table 2: Average pain score in the studied groups before and after intervention

Items	Pre-Menstrual Mean ± SD	Menstrual Mean±SD	Significance test
Pain score before intervention	8.78 ± 1.07	8.66±1.04	t=0.567, P0.572
Pain score after intervention	4.24 ± 1.57	7.20±1.77	t=8.833, *P<0.001*
Paired t test	t=20.857, *P<0.001*	t=6.098, *P<.0001*	

Table 3: Comparison of decrease in pain score after intervention in both groups

Items of the difference in pain score	Premenstrual Group	Menstrual Group
Min max	1.0 - 8.0	0.0 - 5.0
Mean ± SD	4.54 ± 1.54	1.46 ± 1.69
Median	5.0	1.0
Significance test	Mann Whitney test	Z =6.887, *P<0.001*

Table 4: Comparison of percentage decrease in pain score after

Items of the difference in pain score	Premenstrual Group	Menstrual Group
Min max	14.28 - 80.0	0.0 - 62.5
Mean ± SD	51.80 ± 16.88	16.54 ± 19.53
Median	55.56	10.56
Significance test	Mann Whitney test	Z =6.968, P0.000

Table 5: Comparison between length of cycle, duration and amount of menstrual flow before and after intervention in both groups

Time	Items	Premenstrual Group		Menstrual Group		Significance Test
		No	%	No	%	
Length cycle						
Before intervention	21-28 days	30	60.0	33	66.0	X^2=0.39, P0.534
	29-35 days	20	40.0	17	34.0	
After intervention	21-28 days	30	60.0	33	66.0	X^2=0.39, P0.534
	29-35 days	20	40.0	17	34.0	
Duration of menstrual flow						
Before interventio	2-5 days	27	54.0	28	56.0	X^2=0.04, P0.841
	3-8 days	23	46.0	22	44.0	
After intervention	2-5 days	37	74.0	31	62.0	X^2=1.65, P0.198
	3-8 days	13	26.0	19	38.0	
Significance test		X^2=4.34, *P0.03**		X^2=0.37, *P0.542*		
Amount of menstrual flow (Each group 47)						
Before intervention	Low	11	23.4	10	21.3	
	Medium	22	46.8	24	51.1	X^2=0.17, P0.917
	Heavy	14	29.8	13	27.7	
After intervention	Low	13	27.7	11	23.4	
	Medium	25	53.2	26	55.3	X^2=0.24, P0.887
	Heavy	9	19.1	10	21.3	
Significance test		X^2=1.45, *P0.489*		X^2=0.52, *P0.771*		

Table 6: Comparison between associated symptoms before and after intervention in both groups

Associated symptoms	Time	Premenstrual Group		Premenstrual Group		Significance Test
		No	%	No	%	
Fatigue	Before intervention	32	64.0	32	64.0	----------
	After intervention	14	28.0	19	34.0	X^2=1.13, *P0.288*
Significance test		X^2=13.04, *P0.00**		----------		
Vomiting	Before intervention	24	48.0	21	42.0	X^2=0.36, *P0.546*
	After intervention	18	36.0	21	42.0	X^2=0.38, *P0.539*
Significance test		X^2=1.48, *P0.224*		----------		
Diarrhea	Before intervention	24	48.0	12	24.0	X^2=0.21, *P0.648*
	After intervention	18	36.0	12	24.0	X^2=1.71, *P0.190*
Significance test		X^2=0.74, *P0.391*		----------		

DISCUSSION

The current study was done to evaluate the possible effect of administration of NSAIDs before the onset of pain in the anticipating menstrual cycle guided by the concept of preemptive analgesia. This target was significantly supported through the present study. Moreover, the current study may be the first trial for assuming the idea of pain prevention as a method for management of primary dysmenorrhea.

Symptoms associated with menstruation cause a great impact on productivity, and may considered as a bigger contributor to women job absenteeism as shown in the results of Schoep *et al* reported in 2019[17] where 13.8% of all women reported absenteeism during their menstrual periods . In the currunt study the average pain score was high and nearly the same in both groups (8.78 ± 1.07 and 8.66 ± 1.04) quiet enough to affect the social life. There is an urgent need for more focus on the impact of these symptoms.

Different treatment options have been studied for management of primary dysmenorrhea. However, among many alternatives; self-care startigies as consumtion of medications appear to be more convienient for monthly application rather than different techniques like accupauncture and thermal remedies[3,18,19].

Over half of all young women (55%, 95% CI 34.1-74.3) in a systematic review and meta-analysis done by Armour *et al*[20] in 2019 appreciate self-care using both pharmaceutical and non-pharmaceutical options. Among studied medications for dysmenorrhea as paracetamol, oral pills and NSAID, the leaset was supported by a review done by Zahradink *et al.* 2010[21] upon the use of contraceptive pills and considered as the first line therapy.

Mefenamic acid (NSAID) as a medical product, cheap and available with minimal reported side effects on healthy patients was used in the current study .

Pain score was shown to be significantly decreased in the group treated with menfinamic acid before the begining of the cycle standing on the idea of preemptive analgesia[6,7].

Giving mefenamic acid anticipated to block the cycle of enzymes before pain mediators reach the pain receptors whitch aim to block the central sensitization and pain augmentation that may happen after stimulation of pain receptors[8,13].

Concerning the symptoms associated with dysmenorrhea before and after intervention in both groups, the finding of current study revealed that the Percentage of fatigue - as associated symptom- was decreased in both groups after treatment, but the difference was statistically significant among premenstrual treated girls. While percentages of vomiting and diarrhea were not changed after treatment in girls received medication during menstruation, these percentages decreased after intervention in the girls with premenstrual treatment with insignificant difference.

These results in the current study were similar to results obtained in a study published from Iran. This study reported that the most common symptoms associated with dysmenorrhea were physical fatigue and emotional instability manifested as nervousness/ irritability[22].

Menstrual cycle length was not changed in contrary to studies done by Jukic 2008, Uhler 2001 and Athanasiou 1996[23,24,25] who found changes in ovulation and disturbance of the cycle. This is explained by the strategy of giving mefenamic acid only 2 days prior to the anticipated menstruation that is defefintly very far from the time of ovulation.

Some studies were done to evaluate the relation between spasmodic dysmenorrge and central sensitization. Women with dysmenorrhea reported augmented pain sensation to noxious stimulation of the arm and abdomen throughout the menstrual cycle[26]. That's why early management of pain as the main symptoms may alter the process of central sensitization and subsequent chronic pelvic pain and other pain disorderes like fibromyalgia[4].

In a recent published guidelines supported by the Society of Obstetricians and Gynaecologists of Canada Clinical Practice-Gynaecology and CANPAGO Committees and approved by the Board of the SOGC, NSAID was recommended as the first line effective treatment of spasmodic dysmenorrhea. They stated that initiating the dosage should be with the onset of bleeding and /or associated symotoms and usually not required for more than 2 or 3 days. Recommended dosing includes starting with an initial loading dose followed by regular, scheduled dosing up to the recommended daily maximum[27].

In the current study, authors assumed the rationale that earlier initiation of NSAID prior to menstrual pain and symtoms appear. The results supported this justification and giving an open door for new recommendation for such treatment.

On the other hand , A study done by Oladosou *et al* in 2018[28] found that about 18% of women presented

with dysmenorrhea showed no respoonce to NSAIDs as a first line management. Hence, a combination therapy may be adopted in severe resistant cases[15,29].

Our study may explain the relatively limited response as treatment started in all previous studies with the onset of bleeding. However preemptive treatment may avoid comination therapy and the further side effects burden.

CONCLUSION

From this study, it was concluded that NSAIDS can be used effectively to prevent and control primary dysmenorrhea associated symtoms if used before the appearance of symptoms, and targeted groups are in great chance to practice an easier life throughout the entire menstrual cycle.

CONFLICT OF INTEREST

There are no conflicts of interests.

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