Observational Study

Efficacy and safety of fixed dose combination of drotaverine hydrochloride (80 mg) and mefenamic acid (250 mg) *versus* mefenamic acid (250mg) alone in treatment of primary dysmenorrhea : double-blind, randomised comparative study

J B Sharma[1], Alka Kriplani[2], Sunesh Kumar[3], K K Roy[4], Sona Dharmendra[5], Eshani Sharma[6], P Vanamail[7]

To compare the effect of combination of Mefenamic acid and Drotaverine hydrochloride with Mefenamic acid alone in primary dysmenorrhea. Out of 180 women with diagnosis of primary dysmenorrhea 87 women (Group A) were given combination of mefenamic acid 500mg with drotaverine 80 mg, while 93 women (Group B) were given Mefenamic acid 250 mg thrice a day during menstruation. Various pain intensity and relief scores were observed before and after treatment. The baseline characteristics and average pain score were similar. Post treatment pain intensity scores were significantly less in group A as compared to group B (p=0.001). The pain relief scores, patients satisfaction score and clinicians score were significantly higher in group A as compared to group B (p=0.001). Combination of mefenamic acid with drotaverine achieves significantly higher success in pain relief in primary dysmenorrhea as compared to mefenamic acid alone.

[*J Indian Med Assoc* 2018; **116:** 21-6]

Key words **: Primary dysmenorrhea, Mefenamic acid, Drotaverine, pain relief score, patient satisfaction score.**

Primary dysmenorrhea is a very common problem in young women. It is usually defined as cramping pain in the lower abdomen occurring at the onset of menstruation in the absence of any identifiable pelvic disease[1]. It is distinguished from secondary dysmenorrhea, which refers to painful menses resulting from pelvic pathology such as endometriosis. The prevalence rates reported for primary dysmenorrhea vary widely across studies due to the differences in measurement methods and are estimated to be between 40-50% with 30% needing medication and 15% being absent from work[2]. In India, the prevalence of dysmenorrhea has been estimated to be 87.87%[3], while in Malaysia it was 74.5%[4].

The symptoms of primary dysmenorrhea generally last for 2-3 days. The pain is most intense on the first or second day of the menstrual flow, or more precisely the first 24-36 hours, consistent with the time of maximal prostaglandin release into the menstrual fluid[1]. The Pain is suprapubic in location with radiation into the inner aspects of the thighs[1]. Dysmenorrheal pain is suprapubic and spasmodic, and associated with other symptoms like painful menstrual cramps, nausea, vomiting, diarrhoea, fatigue, dizziness and headache and is usually present during adolescence within 6 months to 1 year of menarche[1]. The consequences of untreated primary dysmenorrhea range from school absenteeism to disruption of relationships with family and friends[5,6]. The etiology of primary dysmenorrhea is not precisely understood, but most symptoms can be explained by the action of uterine prostaglandins, particularly $PGF2_{\alpha}$. There is increased endometrial secretion of prostaglandins $F2_{\alpha}$ from sloughed and disintegrating endometrial cell during the menstrual phase in women with primary dysmenorrhea[7].

$PGF2_{\alpha}$ stimulates myometrial contractions, ischemia and sensitization of nerve endings[1]. The clinical evidence for this theory is quite strong. Women who have more severe dysmenorrhea have higher levels of $PGF2_{\alpha}$ in their menstrual fluid[8]. These levels are highest during the first two days of menses, when symptoms peak. In addition, numerous studies have documented the impressive effi-

Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi 110029
[1]MD, FRCOG, PhD, Professor
[2]MD, FRCOG, FAMS Professor and Head
[3]MD Professor and Unit Chief
[4]MD Professor
[5]MSc, SRF
[6]MBBS, SRF
[7]Boistatistician, Ph D Associate Professor

cacy of NSAIDs, which act through prostaglandin synthetase inhibition[9,10].

A focused history and physical examination are usually sufficient to make the diagnosis of primary dysmenorrhea. The history reveals the typical cramping pain with menstruation, and the physical examination is completely normal. Secondary causes of dysmenorrhea must be excluded.

Treatment for primary dysmenorrhea aims to relieve pain or symptoms either by affecting the physiological mechanisms behind menstrual pain (such as prostaglandin production) or by relieving symptoms[11]. Most patients with primary dysmenorrhea show subjective improvement with NSAID treatment. These familiar drugs have a record of efficacy demonstrated by numerous studies over the past 15 years[1,9]. Cochrane Review (2003) also found NSAIDs effective for primary dysmenorrhea[12]. Oral contraceptives work by inhibiting ovulation and provide another effective and well-studied choice for therapy, especially in women desiring birth control[13]. Non-pharmacological treatments include diet, exercise and topical heat. For the approximately 10 percent who do not respond to these options, a host of alternatives exists, ranging from laparoscopic surgery to acupuncture, although with much less evidence to support their use. Mefenamic acid, an anthranilic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID) with demonstrated anti- inflammatory, analgesic and antipyretic activity in laboratory animals. Its mode of action is related to prostaglandin synthetase inhibition. It is widely used in gynecology to treat dysmenorrhea and menorrhagia and for pain relief for minor gynaecological surgeries[14,15]. An antispasmodic and a NSAID, mefenamic acid is believed to be an ideal combination for the treatment of conditions where pain is associated with spasm likely dysmenorrhea. Mefenamic acid inhibits prostaglandin synthesis and drotaverine acts as an antispasmodic. Drotaverine, a benzylisoquinoline derivative, has smooth muscle antispasmodic properties. It is a non-anticholinergic antispasmodic. It relieves smooth muscle spasm by increasing intracellular levels of cyclic-adenosine-monophosphate (cAMP), secondary to inhibition of phosphodiesterase[16-17]. Because of this antispasmodic action, it is widely used in biliary and renal colic, for augmentation of labor, dysmenorrhea and before instrumental diagnostic procedures[14-21]. Drotaverine as a smooth muscle relaxant reduces uterine contraction, which eventually improves uterine blood flow and hypoxia. Drotaverine is also free of the side-effects associated with the known anticholinergic anti-spasmodics like dicyclomine. Drotaverine is non-toxic, its side effects are very minimal and it can be administered even to children[21].

By virtue of two different mechanisms of action due to different active ingredients, a fixed dose combination of drotaverine hydrochloride with mefenamic acid would be expected to provide comprehensive and rapid relief from pain, spasm and/or inflammation in patients of primary dysmenorrhea and the combination of the two seems to be an attractive option. Thus, a study was undertaken to evaluate the effectiveness of fixed dose combination of NSAID (mefenamic acid) and antispasmodic (drotaverine hydrochloride) in women with primary dysmenorrhea as compared to mefenamic acid alone.

Materials and Methods

The present study was undertaken at the department of Obstetrics and Gynaecology department, in a tertiary referral centre, All India Institute of Medical Sciences, New Delhi after due approval of the ethical committee of the institute (Ref No IEC/NP-383/08-10-2014). The study was conducted from May 2015 to December 2016. The randomised controlled trial was registered with the CTRI number CTRI/2015/05/005796.

The sample size calculated with the help of biostatistician with 5% error and 90% power, was 140, with 25% loss to follow up, a sample size of 180 was taken. A total of 180 women aged 18-35 years with regular menstruation with complaints of primary dysmenorrhea and who were willing to participate in the study and were ready to come for follow up and signed written informed consent were enrolled in the study. The exclusion criteria were women (secondary dysmenorrhea), pregnancy, lactation, any medical disorder or on medication, premenstrual syndrome, infertility, with intrauterine device or oral contraceptive pill or patients not willing to participate in the study. Women fulfilling the criteria were randomised using computer generated randomisation number into two groups. Group A (87 women) were given a fixed dose combination of drotaverine hydrochloride (80mg) with mefenamic acid (250 mg) thrice a day starting on the first day of the menstrual cycle and continued for the whole menstrual cycle (for 5 days). Group B were given Mefenamic acid (250 mg) thrice a day starting on the first day of the menstrual cycle and continued for the whole menstrual cycle (for 5 days). The characteristics of women were noted in both the groups. Mean pain intensity score was calculated at the baseline using 11 point pain intensity numerical rating scale (PI-NRS) with 0 being no pain and 10 means worst pain. The 11 point intensity numerical rating scale was given after the start of the therapy at 15minutes, 30minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours (on phone). The mean pain relief score between the two groups was also recorded at the baseline and after the therapy. Patients were kept in outpatient department for first 2 hours during which time the pain score was recorded by the research fellow. The patient was then

given a diary and taught to fill the pain intensity score and pain relief scores at 4, 8, 12, 24 and 48 hours at home. All patients were asked to come to hospital again between 5-10 days (mean 7th day) with the diary. The investigator assessed the patient self reported pain intensity and pain relief, medication compliance, concomitant medicines and any adverse reactions. At this time, 5 point patient satisfaction score and clinicians score (0=poor, 1= fair, 2=good, 3= very good, 4= excellent) were recorded for all the patients. Total area under pain relief score (TOPAR) was calculated at 2, 4 and 8 hours. Sum of pain intensity difference (SPID) was calculated at 2, 4 and 8 hours. Peak pain intensity difference was also calculated at 2, 4 and 8 hours. Pain relief was also calculated at 4 and 8 hours. Any adverse effects were noted in all the cases.

Statistical Analysis :

Statistical analyses were done based per protocol method in which patients lost to follow-up and those did not receive treatment were excluded from the analysis. Continuous data were subjected to Kolmogorov-Smirnov test to confirm whether the data follows normal distribution. Descriptive statistics such as mean, standard deviation (sd) and range values were calculated for normally distributed data. Comparisons of mean values of pain intensity score and pain relief scores between two groups were carried out using Student's t-independent test. Changes in pain intensity and pain relief scores from baseline to different follow-up times within the group were tested using Student's t-paired test. Further, repeated measures analysis of variance was carried out to correct the effect of drug while excluding the influence of base-line values. Spearman's rank correlation coefficient was computed between patients' satisfaction score and clinician's score. Frequencies of various adverse reactions by drug groups were compared using Chi-square/Fisher's Exact test as appropriate. For all statistical tests a two tailed probability of $P<0.05$ was considered for statistical significance. Statistical package for services solution (SPSS) IBM version 21.0 was used for data analysis.

Results :

Out of total of 180 women enrolled in the study, there were 87 women (48.3%) in group A, and 93 women (52.7%) in group B. The baseline characteristics of women in the two groups are shown in Table 1. Thus, the average age, body mass index (BMI), pain radiating to thigh, headache were similar in two groups. The average ±SD pain score at baseline was 5.55±0.49 in group A and 5.60±0.49 in group B and was not significantly different (p=0.496).

Table 2 shows comparison of mean pain intensity score between the two groups using 'T' tests before treatment, and at varying times (15 minutes, 30 minutes, 1 hour, 2 hour, 4 hours, 8 hours, 12 hours, 24 hours and 48 hours) after treatment. Thus the pretreatment and 15 minutes post treatment mean pain intensity score in the two groups was similar. (p=0.274, p=0.167). However, the mean pain intensity score at 30 minutes, 1 hour, 2 hour, 4 hour, 8 hour, 12 hours, 24 hours and 48 hours was significantly less in group A (drotaverine and mefenamic acid combination) as compared to group B (mefenamic acid alone) (p=0.001). Fig 1 gives diagrammatic representation of estimated marginal means of pain intensity using repeated measures of ANOVA model showing that pain intensity score was higher in group B as compared to group A.

Table 1 — *Comparison of base-line characteristics in terms of means/ percent values between the Groups*

Variables	Group A (n=87)	Group B (n=93)	P-value
Average Age±SD (years)	24.86±4.25	24.30±4.67	0.402*
Range values	18-35	13-35	
Average BMI±SD (Kg/m^2)	20.97±1.38	20.86±1.38	0.592*
Range values	16.5-24.3	17.2-24.1	
Pain radiating thigh (n, %)	33 (37.9)	30 (32.3)	0.425$
Head ache (n, %)	17 (19.5)	13 (14)	0.317$
Average ± SD Pain score in the last six month	5.55±0.50	5.60±0.49	0.496*
Range values	5-6	5-6	

*- based on Student's t-independent test
$- based on Chi-square test

Table 2 — *Comparison of mean pain intensity scores between the groups at each time point using T-Test*

Time point	Group A (n=87)	Group B (n=93)	P-Value
Pre treatment	9.40±0.49	9.48±0.50	0.274
Post-treatment at 15 minutes	9.00±0.66	9.14±0.68	0.167
Post-treatment at 30 minutes	7.44±0.52	7.95±0.73	0.001
Post-treatment at 1 hour	6.47±0.52	6.87±0.63	0.001
Post-treatment at 2 hours	5.49±0.53	6.13±0.56	0.001
Post-treatment at 4 hours	4.58±0.52	5.55±0.50	0.001
Post-treatment at 8 hours	4.09±0.68	5.08±0.61	0.001
Post-treatment at 12 hours	3.24±0.63	4.11±0.58	0.001
Post-treatment at 24 hours	1.67±0.69	3.03±0.09	0.001
Post-treatment at 48 hours	0.72±0.68	1.31±0.97	0.001

Table 3 shows comparison of mean pain relief scores between the two groups using T test. Thus the mean relief score at 15 minutes in the two groups was similar (p=0.167). However, the mean pain relief score was significantly higher in group A as compared to group B at 30 minute, 1 hour, 2 hour, 4 hour, 8 hour, 12 hour, 24 hours and 48 hours (p=0.001). Fig 2 gives diagrammatic representation of estimated marginal mean of pain relief in the two groups showing that pain relief at 30 minutes and later was significantly higher in group A than in group B.

Table 4 shows comparison of mean values of face score difference, patient satisfaction score and clinicians score between the two groups using T test. Score was significantly higher in group A (4.25±0.45) as compared to group B (3.26±0.92) (p=0.001). Patients satisfaction score was also significantly higher in group A (2.62±0.58) as com-

Table 3— *Comparison of mean relief scores between the groups at each time point using T-Test*

Time point	Group A (n=87)	Group B (n=93)	P-Value
Post-treatment at 15 minutes	1.00±0.66	0.86±0.68	0.167
Post-treatment at 30 minutes	2.56±0.52	2.05±0.73	0.001
Post-treatment at 1 hour	3.53±0.52	3.13±0.63	0.001
Post-treatment at 2 hours	4.51±0.53	3.87±0.56	0.001
Post-treatment at 4 hours	5.43±0.52	4.45±0.50	0.001
Post-treatment at 8 hours	5.91±0.67	4.93±0.61	0.001
Post-treatment at 12 hours	6.76±0.63	5.89±0.58	0.001
Post-treatment at 24 hours	8.33±0.69	6.97±0.83	0.001
Post-treatment at 48 hours	9.28±0.68	8.69±0.97	0.001

Table 4 — *Comparison of mean values of face score difference (pre-final), patient's satisfaction score and clinician's score between the groups using T-Test*

Score Types	Group A (n=87)	Group B (n=93)	P-Value
Face score difference	4.25±0.65	3.26±0.92	0.001
Patient's satisfaction score	2.62±0.58	1.81±0.68	0.001
Clinician's score	2.71±0.53	1.73±0.65	0.001

Group A : Spearman's correlation coefficient between patient score and clinician's score = 0.289 (P=0.007).
Group B : Spearman's correlation coefficient between patient score and clinician's score = 0.376 (P=0.001).

pared to group B (1.81±0.68) (p=0.001). Similarly clinicians score was also significantly higher in group A (2.71± 0.53) as compared to group B (1.73±0.65) (p=0.001).

Table 5 shows comparison of efficacy parameters between the two groups. Thus the total area under pain relief (TOPAR) score at 2, 4 and 8 hours was significantly higher in group A (11.60±1.57, 17.02±1.86, 22.93±2.09) as compared to group B (9.91±2.03, 14.37±2.316, 19.29±2.479) (p=0.001).

Sum of pain intensity difference (PID) at 2, 4 and 8 hours was also higher within group A (9.21±2.59, 14.03±3.18, 19.34±3.71) than in group B (7.85±2.84, 11.78±3.378, 16.19±3.834) (p=0.001).

Peak pain intensity difference (peak PID) at 2, 4 and 8 hours was also significant higher in group A (3.91±0.757, 4.83±0.74, 5.36±0.79) as compared to group B (3.37±0.374, 3.95±0.682, 4.49±0.686) p=0.001.

Peak pain relief at 2, 4 and 8 hours was also significant

Table 5 — *Comparison of efficacy parameters between the two groups*

Efficacy parameters	Group A (N=87)		Group B (N=93)		P-Value
	Mean	SD	Mean	SD	
TOPAR-2hrs	11.60	1.573	9.91	2.031	0.001
TOPAR-4hrs	17.02	1.86	14.37	2.316	0.001
TOPAR-8hrs	22.93	2.09	19.29	2.479	0.001
SPID-2hrs	9.21	2.598	7.82	2.840	0.001
SPID-4hrs	14.03	3.18	11.78	3.378	0.001
SPID-8hrs	19.34	3.71	16.19	3.834	0.001
PEAK-PID/2hrs	3.91	0.757	3.37	0.734	0.001
PEAK-PID/4hrs	4.83	0.74	3.95	0.682	0.001
PEAK-PID/8hrs	5.36	0.79	4.49	0.686	0.001
PEAK-PR/2hrs	4.51	0.525	3.88	0.549	0.001
PEAK-PR/4hrs	5.43	0.52	4.46	0.501	0.001
PEAK-PR/8hrs	5.95	0.65	5.01	0.542	0.01

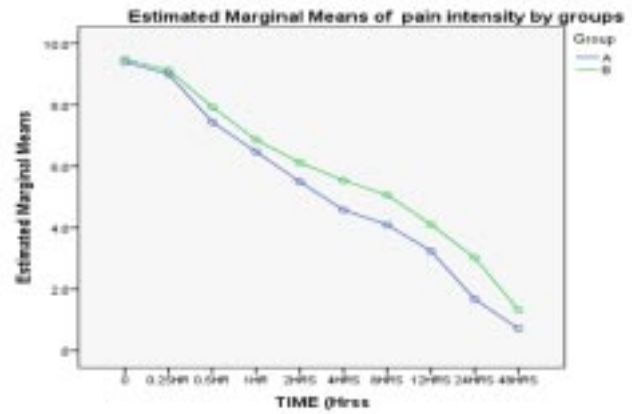

Fig 1 — Comparison of estimated Marginal Means using Repeated measures of ANOVA model

higher in group A (4.51±0.525, 5.43±0.52, 5.95±0.65) than in group B (3.88±0.549, 4.46±0.501, 5.01±0.542) (p=0.001).

Fig 3 gives diagrammatic representation of patients and clinicians response about the study drugs in two groups and shows results in group A as compared to group B.

Hence although mefenamic acid alone was also effective in controlling symptoms of dysmenorrhea, the addition of drotaverine to mefenamic acid improves the results in most cases. Hence combination of drotaverine and mefenamic acid was more effective in management of primary dysmenorrhea than mefenamic acid alone.

Discussion

Primary dysmenorrhea is defined as painful menstruation without any evident pathology for it[1]. Its prevalence varies from 40-50% with 15% rate of absenteeism from work or school[2,3]. There is increased abnormal uterine contractility due to increased menstrual endometrial secretion of menstrual prostaglandins F2α in women suffering from primary dysmenorrhea. Management includes pharmaco-

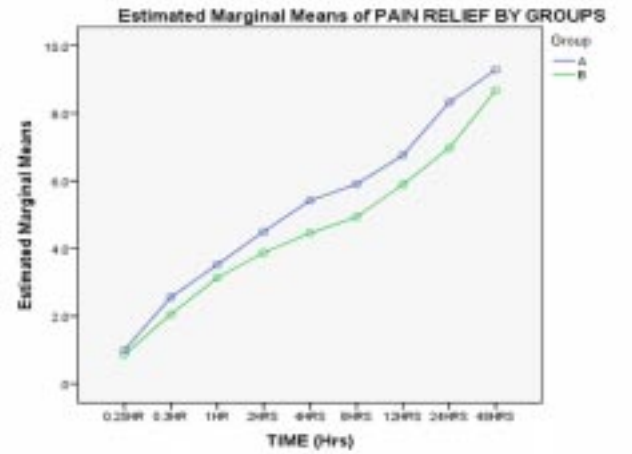

Fig 2 — Comparison of estimated Marginal Means using Repeated measures of ANOVA model

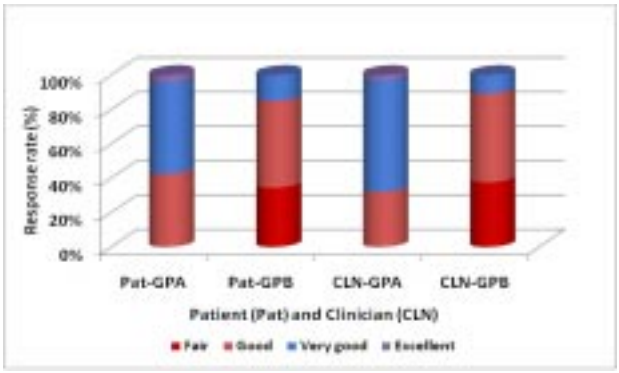

Fig 3 — Patients' and clinician's response about the study drugs

logical, non pharmacological and surgical methods. Most common treatment is use of non steroidal anti inflammatory drugs (NSAID) like mefenamic acid, aceclofenac, ibuprofen, naproxen given during menstruation. They act by inhibiting prostaglandin secretion which is the causative factor in primary dysmenorrhea[1,11,12]. Studies including Cochrane review have proven the efficacy of NSAID's in symptomatic relief in primary dysmenorrhea[10,12]. Drotaverine is an anti-spasmodic drug used for renal colic, abdominal colicy, pain, labour pains[16-21]. As there is spasmodic pain in primary dysmenorrhea, drotaverine should provide additional relief in its management when combined with mefenamic acid.

The results of the present study confirm that both mefenamic acid alone and combination of mefenamic acid and drotaverine hydrochloride are effective for pain relief in dysmenorrhea, but the combination therapy (mefenamic acid and drotaverine) was superior as compared to mefenamic acid alone. Thus the mean pain intensity score was significantly lower and mean pain relief score was significantly higher in group A (combination group) than in group B (mefenamic acid alone) (p=0.001).

The patient satisfaction score and clinicians score were significantly higher with combination therapy than mefenamic acid alone (p=0.001). The combination was also significantly superior to monotherapy in terms of total area under pain relief score (TOPAR 2, 4 and 8), (p=0.001), sum of pain intensity difference (2, 4 to 8 hours). (SPID 2, 4 to 8 hours) p=0.001, peak pain intensity difference (2, 4 to 8 hours) p=0.001 and peak pain relief at 2, 4 to 8 hours (PR 2, 4 to 8). Both treatments were well tolerated by all patients.

NSAIDs remain first choice of treatment for primary dysmenorrrhea with relief in as many as 80-85% of primary dysmenorrhea patients[1]. If relief is inadequate, combination oral contraceptive can be tried for upto 3 months[1]. If both NSAID and combined pill do not provide relief (only few cases), then diagnostic laparoscopy can be performed for finding any cause of secondary dysmenorrhea like endometriosis which doesn't respond to NSIAD's. The cause can also be treated at the same time by electrofulguration of endometriosis and adhesiolysis. Hysteroscopy and cervical dilation can be done along with laparoscopy which may help in widening the cervical canal promoting menstrual flow and thus reducing menstrual fluid prostaglandin contact with the myometrium. In addition, cervical dilation may induce partial disruption of paracervical innervation helping in pain relief.

In the present study, mefenamic acid, a prostaglandin inhibitor (NSAID's) exerted its anti-inflammatory activity by inhibition of prostaglandin synthesis and thus relieving pain of dysmenorrhea while drotaverine, an antispasmodic, produces rapid pain relief due to its antispasmodic effect. Mefenamic acid provides sustained analgesic effect in painful spasms of pelvic and abdominal origin. Thus the combination of mefenamic acid and drotaverine provides superior pain relief than mefenamic acid alone.

To conclude the combination of mefenamic acid and drotaverine provides superior and significantly higher pain relief for the medical management of primary dysmenorrhea than mefenamic acid. However, large multicentric randomized controlled trials are needed before recommendation of combination of drotaverine and mefenamic acid in the treatment of primary dysmenorrhea.

Acknowledgement :

The authors are thankful to Walter Bushnell Pvt Ltd. New Delhi for providing free drugs for this trial but they had no influence on the study or its results and were not shown the results. The authors are thankful to all the faculty, residents, nursing staff and patients for their help in this study.

Compliance with Ethical Requirements and Conflict of Interest

All procedures followed were in accordance with the Ethical Standard of the Responsible Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all the patients. The study was conducted in department of Obstetrics and Gynaecology. The work was designed and performed after taking ethical clearance from the Institutional ethical committee. The study was funded by Walter Bushnell Pvt Ltd.

Registration number : CTRI Number: CTRI/2015/05/00579

References

1 Dawood MY — Primary dysmenorrhea: advances in pathogenesis and management. *Obstet Gynecol* 2006; **108:** 428-41.
2 Burnett MA, Antao V, Black A, Feldman K, Grenville A, Lea R,

Lefebvre G, Pinsonneault O, Robert M — Prevalence of primary dysmenorrhea in Canada. *J Obstet Gynaecol Can* 2005; **27:** 765-70.
3 Agarwal AK, Agarwal A — A study of dysmenorrhea during menstruation in adolescent girls. *Indian J Community Med* 2010; **35:** 159-64.
4 Wong LP, Khoo EM — Dysmenorrhea in a multiethnic population of adolescent Asian girls. *Int J Gynecol Obstet* 2010; **108:** 139-42.
5 Eryilmaz G, Ozdemir F, Pasinlioglu T — Dysmenorrhea prevalence among adolescents in eastern Turkey: Its effect on school performance and relationships with family and friends. *J Pediatr Adolesc Gynecol* 2010; **23:** 267-72.
6 Titilayo A, Agunbiade OM, Banjo O — Menstrual discomfort and its influence on daily academic activities and psychosocial relationship among undergraduate female students in Nigeria. *Tanzan J Health Res* 2009; **11:** 181-8.
7 Powell AM, Chan WY, Alvin P — Menstrual-PGF2 alpha, PGE2 and TXA2 in normal and dysmenorrheic women and their temporal relationship to dysmenorrhea. *Prostaglandins* 1985; **29:** 273-90.
8 Chan WY, Dawood MY, Fuchs F — Prostaglandins in primary dysmenorrhea. Comparison of prophylactic and nonprophylactic treatment with ibuprofen and use of oral contraceptives. *Am J Med* 1981; **70:** 535-41.
9 Dawood MY — Ibuprofen and dysmenorrhea. *Am J Med* 1984; **77:** 87-94.
10 Pareek A, Chandurkar NB, Patil RT — Efficacy and safety of aceclofenac and drotaverine fixed-dose combination in the treatment of primary dysmenorrhoea: a double-blind, double-dummy, randomized comparative study with aceclofenac. *Eur J Obstet Gynecol Reprod Biol* 2010; **152:** 86-90.
11 Proctor. M Diagnosis and management of dysmenorrhea, *BMJ* 2006; **332:** 1134-8.
12 Marjoribanks J, Proctor ML, Farquhar C — Nonsteroidal anti-inflammatory drugs for primary dysmenorrhea (Cochrane Review). 2003; 4: CD001751. In: The Cochrane Library, Issue 4, 2003, Oxford: Update Software.
13 Proctor ML, Roberts H, Farquhar CM — Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhea (Cochrane Review). 2001;(4):CD002120. In: The Cochrane Library, Issue 4, 2001, Oxford: Update Software.
14 Sharma JB — Comparison of efficacy of oral Drotaverine plus mefenamic acid with paracervical block and with intravenous sedation for pain relief during hysteroscopy and endometrial biopsy. *Indian J Med Sci* 2009; **63:**
15 Budoff PW — Use of mefenamic acid in the treatment of primary dysmenorrhea. *JAMA* 1979; **241:** 2713-6.
16 Pap A, Topa L, Balgha V — Drotaverine antagonizes spasm of Oddi's sphincter provoked by morphine in man. *Gastroenterology* 1997; **112:** A519
17 Bolaji OO, Onyeji CO, Ogunaini AO — Pharmacokinetics and bioavailability of drotaverine in humans. *Eur J Drug Metab Pharmacokinet* 1996; **21:** 217-21.
18 Romics I, Molnar DL, Timberg G — The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int* 2003; **92:** 92-6.
19 Sharma JB, Pundir P, Kumar A — Drotaverine hydrochloride Vs Valethamate bromide in acceleration of labor. *Int J Gynecol Obstet* 2001; **4:** 43-8.
20 Singh KC, Jain P, Goel N — Drotaverine hydrochloride for augmentation of labor. *Int J Gynecol Obstet* 2004; **84:** 17-22.
21 Blasko G — Pharmocology: a mechanism of action and clinical significance of a convenient antispasmodic agent: Drotaverine. *J Am Med Assoc Ind Physcians Update* 1998; **1:** 63-9.