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Oral Drotaverine and Aceclofenac Combination versus Aceclofenac alone for Postoperative Pain Relief: A Prospective Randomized Clinical Trial

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ABSTRACT

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Objective: To compare the efficacy of Drotaverine- Aceclofenac combination with Aceclofenac alone in treatment of postoperative spasm and pain.

Methods: In a prospective Randomized Clinical Trial, patients undergoing laparoscopic surgeries not involving bowel resections were enrolled. Group 1 received 80 mg Drotaverine and 100 mg Aceclofenac combination while Group 2 received 100 mg Aceclofenac alone. Pain was assessed by a 10-point visual analog scale on day 1, 3 and 5 after surgery.

Results: We recruited 70 cases in each group. Group 1 showed statistically significant reduction in pain scores at day 1, 3 and 5, postoperatively. The scores for Global assessment and general evaluation by doctor were statistically higher in group 1. Group 1 also experienced relatively less adverse events.

Conclusion: Drotaverine with Aceclofenac combination is more effective than Aceclofenac alone in treatment of postoperative pain after laparoscopic procedures which do not involve bowel resections or extensive bowel handling.

Keywords: Drotaverine, Aceclofenac, laparoscopic surgery, pain relief.

INTRODUCTION

Post-operative pain is multifactorial. Apart from the surgical trauma to the abdominal wall, visceral pain or deep intra-abdominal pain accounts for a significant amount of discomfort during the post-operative period, more so in laparoscopic surgery. Muscle spasm is also a common cause of pain in the postoperative period. This pain probably results partially from the direct effect of muscle spasms in stimulating mechanosensitive pain receptors. The indirect effect of muscle spasm also compresses the blood vessels and cause ischemia.[1] Thus pain and smooth muscle spasm sets in a vicious cycle. Involved in the vicious cycle is the arachidonic acid cascade, which leads to the formation of prostaglandins, which are the important mediators of spasmogenic response of smooth muscles. Inhibition of cascade is therefore important to the control of spasm and pain.

Antispasmodic agents relive the spasm of smooth muscles and there by pain. Drotaverine Hydrochloride is a well established directly acting, smooth muscle anti-spasmodic that brings about quick and effective pain relief by inhibiting enzyme phosphodiesterase IV and calmodulin. It is devoid of any anticholinergic side effects.[2] To counter the pain component unrelated to spasm or secondary spasm where several inflammatory mediators are involved, the Non-Steroidal Anti-Inflammatory Drugs (NSAID's) provide relief. A combination of Drotaverine with an effective and relatively longer acting NSAID which has established safety and no interaction with Drotaverine would be an effective therapeutic strategy for sustained pain relief. The choice of NSAIDs in clinical practice mostly depends on their analgesic potencies, the adverse effect profile, and their cost. Aceclofenac is a novel, long acting, well tolerated NSAID with lower incidence of side effects and established safety profile which provides sustained pain relief by preferentially blocking COX (Cyclo-oxygenase) II enzyme, making it an ideal NSAID for combining with fast acting Drotaverine, for effective pain relief from post-operative procedures.[3]The relative efficacies of the two drugs are therefore complimentary for effective pain relief as has been shown in previous trials.[4]The aim of the present study is to compare the efficacy of pain relief and adverse effects profile of a single NSAID drug (Aceclofenac) versus a combination of the same NSAID combined with a potent antispasmodic (Drotavarine) in patients undergoing laparoscopic procedures involving hollow visceral organs.

MATERIALS AND METHODS

The Ethics Committee of Sir Gangaram Hospital (IRB) approved this open-label, randomized clinical trial. The trial was conducted in accordance with the ethical standards on human experimentation as per the Helsinki declaration of 1975 (revised in 1983). The study was registered in the Clinical Trial Registry of India (CTRI) before undertaking the trial.

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Both male and female patients between 18 and 60 years of age admitted for laparoscopic surgeries of hollow visceral organs not necessitating restriction of oral feeds were recruited. Because both the drugs had o be given orally, procedures needing bowel resection or extensive bowel handling were excluded from this study that would have precluded early resumption of feeding. The exclusion criteria are mentioned in Table I. Randomization was done by a computer-generated sequence, with the help of the software www.randomization.com, and stored in sealed opaque envelopes.

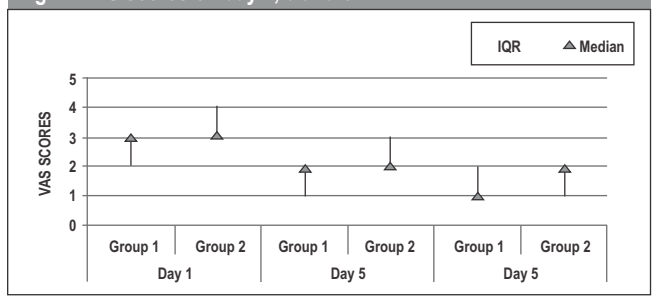
Table I: Exclusion criteria

1.	Any open abdominal surgery where oral intake is not allowed.
2.	Patients having peptic ulcer disease/ bleeding disorders/hepatic and renal dysfunctions.
3.	Known hypersensitivity to any one of the active ingredients/excipients
4.	Any active cancer
5.	Chronic diseases or recent CV events (diabetes mellitus/hypertension)
6.	Psychotic disorders, dementia, mental retardation (Suspects who are not weakly and mentally able to personally consent for participating in this study are not eligible).

After detailed explanation of the study and involved procedures to the patients, a written informed consent was obtained. Subsequently, the patients were randomly allocated to the two treatment regimens according to their enrolled case numbers. The patients received either 100 mg of aceclofenac in combination with 80 mg of drotaverine (Group 1) or 100 mg of aceclofenac (Group 2) per os (p.o.) by random allocation. The recommended adult dose of aceclofenac is 200 mg daily taken as two separate 100 mg doses and that of drotavarine is 40 to 80 mg upto three times daily. There are no reported drug interactions between the two and are availavble as fixed dose combination. The pain intensity scores (VAS scores) of the patients in both the groups were recorded as per visual analog scale (VAS) (Fig. 1)by direct questioning the patients at 24 hours (Day 1), on day 3and day 5post-operatively. Rescue analgesics were offered as concomitant medications if insufficient analgesia was achieved.

The outcomes of the patients and any adverse events to the treatment were also noted. A Global Assessment Score was calculated and tabulated. Score 0,1,2,3 was given to the response: 'Not Effective', 'Mild Effective', 'Moderately Effective' and 'Very Effective' respectively. General Evaluation, based on the clinical assessment by the Doctor was given score0, 1 and 2 as per the following states: Worse, Same and Improved, respectively.

Fig. 1: VAS scores on day 1, 3 and 5



Statistical analysis was performed by the SPSS program for Windows, version 17.0. Data was checked for normality before statistical analysis using ShaiproWilk test. Continuous variables are presented as mean ± Standard Deviation (SD) or Median Interquartile Range (IQR) if the data is non-normal, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test to compare their relative efficacies. Nominal categorical data between the groups were compared using Chi-square test as appropriate. Non-normal distribution continuous variables were compared using Man Whitney U test and for all statistical tests, a p value less than 0.05 was taken to indicate a significant difference. A Sample size of 70 per group was calculated based on a difference of 1 in patients' VAS scores between groups, a population variance of $(2)^2$, a two-sided α of 0.05, and a power of 80%.

RESULTS

A total of 140 patients who underwent laparoscopic procedures including cholecystectomy, appendicectomy, nephrolithotomy or ureterolithotomy were randomized into two groups i.e. Group 1 & Group 2.There were no drop outs till the completion of the study. The groups were comparable with respect to age and sex (Table 2, Table 3). Rescue analgesics were not given to any of the patient in either of the group.

Following the administration of the drugs there was gradual reduction in VAS scores in both the groups, however the median VAS score was significantly low in Group 1($P<0.05$) on Day 1, Day 3 and Day 5 as compared to Group 2 (Fig. 1). Although the median VAS scores in the two groups were 3,2 and 1 in Group 1 and 3,2 and 2 in Group 2, the Inter Quartile Range resulted in significant difference in VAS scores in the two groups. Adverse events like nausea, vomiting, dizziness and diarrhoea were reported in both the groups however, their occurrence was significantly higher in group 2($P<0.05$), as compared to Group 1(Fig. 2). The scores for Global assessment scores and General evaluation by Doctor were significantlyhigher($P<0.05$) in Group 1 than Group 2 (Fig 3).

Table 2: Distribution of Patients into Group 1 and Group 2

Group	Number of patients	%
Group	170	50%
Group	270	50%
Total	140	100%

Table 3: Distribution of Patients according to age (p<0.05)

	Group 1		Group 2	
	Mean ± SD	Min - Max	Mean ± SD	Min - Max
Age	42.59 ± 13.3	89 - 68	44.04 ± 12.77	22 - 72

Fig. 2: Incidence of Adverse events

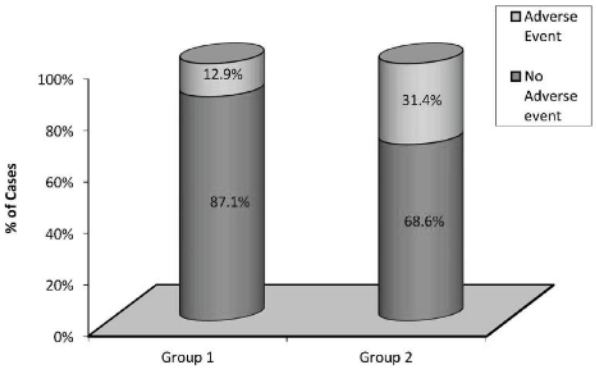
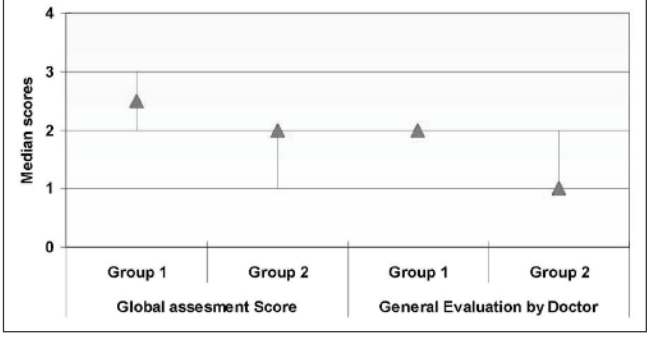


Fig. 3: Global assessment score and general evaluation by doctor (p<0.05)



DISCUSSION

Drotaverine hydrochloride, an isoquinoline derivative, is a potent spasmolytic drug which acts directly on the smooth muscles by inhibiting phosphodiesterase IV enzyme & Calmodulin. It is devoid of any anticholinergic side effects unlike other available spasmolytics like dicyclomine. Because of this anti-spasmodic action, it is widely used in biliary, renal and ureteric colic, for augmentation of labor, dysmenorrhea, and before instrumental diagnostic procedures.[2,-6] Onset of pain relief is observed in 12 minutes when Drotaverine is administered orally.[7] It can be safely co-administered with other drugs and provide comprehensive pain relief when combined with analgesic and anti-inflammatory drugs.[8] Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (COX), preferentially COX II which is involved in the production of prostaglandins**.** It has superior anti-inflammatory properties and an improved safety profile than conventional NSAIDs with respect to adverse effects on gastrointestinal and cardiovascular system.[9,10]

Combination of NSAIDs and antispasmodics is a promising approach to relieve post-operative pain associated with spasm and inflammation. Drotaverineproduces rapid pain relief due to antispasmodic action while Aceclofenac provides sustained analgesic effect. A fixed dose combination of Drotaverine with Aceclofenac is an effective and well tolerated therapy. Not only does it provides desired control of pain that is the primary aim of the treatment, but also controls inflammation and may contribute to healing process after abdominal operations. Combination of NSAIDs and antispasmodics has an established efficacy in most gynecological procedures and minor surgeries.[11,12] The occurrence of postoperative pain and its intensity is influenced by the type of surgical procedures. In some of the laparoscopic surgeries which do not involve bowel resections or extensive bowel handling, early oral feeding can be initiated on return of bowel sounds owing to early postoperative recovery. Early administration of oral analgesics is possible in this group of surgeries. Therefore patients undergoing laparoscopic surgeries not necessitating prolonged bowel rest post-operatively were chosen for this study.

This study although the first of its kind demonstrates the benefits of Drotaverine and Aceclofenac combination in these selected group of patients. The efficacy and safety of this combination, has already been proved in dysmenorrhea.[4] In this study although both the groups had shown good results with regard to pain scores however, the Group 1 showed significantly better resolution of postoperative pain because of comprehensive relief from pain associated with spasm and inflammation. Early resolution of pain would mean early ambulation, faster recovery and earlier return to normal activities.

Trauma and pain increase the levels of circulating catecholamines, which stimulate nausea and vomiting. [13] It is a common finding that injured patients exhibit nausea as well as pain. Complete pain relief without relief of nausea is far less frequent (9.5 %). Conversely, when pain relief is inadequate, nausea persists.[14] In the present study adverse events like nausea, vomiting, dizziness etc. were considerably less in group 1 because of better pain relief than group 2. General

evaluation by the doctor as per the questionnaire and Global Assessment Scores were also significantly higher ($P<0.05$)in Group 1 than Group 2. This study therefore shows that with minimal side effects the combination of oral Drotaverine and Aceclofenac can be recommended for oral analgesia following laparoscopic surgeries which do not involve extensive bowel handling.

CONCLUSION

Clinicians have always been on the lookout for better analgesia for expediting recovery in patients in the postoperative period. The present study showed that oral combination of drotaverine with aceclofenac is significantly more effective than aceclofenac alone in relieving postoperative pain following laparoscopic surgeries which do not involve bowel resections or extensive bowel handling like cholecystectomy, appendicectomy, nephrolithotomy or ureterolithotomy. The combination provides fairly early onset of pain relief and is well tolerated with minimal side effects.

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REFERENCES

1. Guyton A C, Hall J E . *Textbook of Medical Physiology*. 11th edition, El-Sevier Saunders, USA, 2006, p-599.
2. Blasko G. Pharmacology: a mechanism of action and clinical significance of a convenient antispasmodic agent: Drotaverine. *J Am Med Assoc India* 1998; 1: 63-9.
3. Brogden R N et al. Aceclofenac. A review of its pharmacodynamic properties and therapeutic potential in the treatment of rheumatic disorders and in pain management. *Drugs* 1996; 52(1):113-24.
4. PareekA et al. 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 ObstetGynecolReprod Biol*. 2010; 152(1): 86-90.
5. Romics I, Molnar DL, Timberg G, Mrklic B, Jelakovic B, Koszegis G, et al. The effect of drotaverine hydrochloride in acute colicky pain caused by renal and ureteric stones. *BJU Int* 2003; 92:92-6.
6. Sharma JB, Pundir P, Kumar A, Murthy NS. Drotaverine hydrochloride Vs Valethamate bromide in acceleration of labor. *Int J GynecolObstet* 2001; 4: 43-8.
7. Dawood MY. Drugs, Akos Pap "The management of smooth muscle spasm". OnixNyomadaKft, Hungary., 1981; 22: 42-56.
8. Singh KC, Jain P, Goel N, Saxena A. Drotaverine hydrochloride for augmentation of labor. *Int J GynecolObstet* 2004; 84:17-22.
9. Dooley et al. Aceclofenac: A Reappraisal of its Use in the Management of Pain and Rheumatic Disease. *Drugs* 2001; 61(9): 1351-78.
10. Brogden R N et al. Aceclofenac. A review of its pharmacodynamic properties and therapeutic potential in the treatment of rheumatic disorders and in pain management. *Drugs* 1996; 52(1):113-24.
11. Sharma J B et al. Comparison of efficacy of oral Drotaverine plus mefenamic acid with paracervical block and with intravenous sedation for pain relief during hystereoscopy and endometrial biopsy. *Indian J Med Sci* 2009; 63(6): 244-52.
12. Sharma J B. Efficacy of oral Drotaverine plus mefenamic acid for painless insertion of intra-uterine contraceptive device in outpatient setting. *FOGSI* 2012.
13. Jenkins L.C., Lahay D., Central mechanisms of vomiting related to catecholamine response: Anaesthetic implication. *Canad Anaesth Soc J* 1971;18:434.
14. Andersen R et al. Pain as a major cause of postoperative nausea. *Canad Anaesth Soc J* 1976; 23(4): 366-69.