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ORIGINAL ARTICLE

Results Of Two Multicentric, Comparative, Randomized, Parallel Group Clinical Trials To Evaluate The Efficacy And Safety Of Dexketoprofen Trometamol In The Treatment Of Dental Pain And Dysmenorrhoea In Indian Patients

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ABSTRACT

Background*:* Dexketoprofen is the active enantiomer of the popular NSAID Ketoprofen which is a 50:50 mixture of S (+) and R (-) enantiomers.
Aims: To demonstrate therapeutic efficacy and safety of Dexketoprofen 25 mg as compared to Ketoprofen 50 mg in patients undergoing dental surgery and in patients with dysmenorrhoea.
Study Design: Multicentric, comparative, randomized, parallel group studies.
Materials and Methods: Out patients undergoing third molar extraction were randomized to receive either Dexketoprofen or Ketoprofen. In a separate study, patients with dysmenorrhoea were randomized into similar two groups. Pain intensity as recorded on Visual Analogue Scale before therapy and at regular intervals after therapy was quantified and statistically analysed.
Results: In both the studies, the groups were comparable in demographics and baseline pain intensity. Dexketoprofen was as effective as Ketoprofen in relieving pain during menstruation. In case of dental pain, Dexketoprofen provided early onset of statistically significant analgesia as compared to Ketoprofen.
Conclusions: Dexketoprofen (25mg) is as effective as Ketoprofen (50mg) in the treatment of dysmenorrhoea and is a faster and equally safe analgesic in the treatment of acute pain of dental surgery.

Key words: Dexketoprofen, Ketoprofen, Dental extraction, Dysmenorrhoea

Key Messages

[1] Chirally pure drugs provide the active ingredient of the drug minus the inactive and sometimes toxic ingredient, thus decreasing the metabolic load on the body, decreasing the side effects and at the same time providing equal or better therapeutic efficacy at half the dose.
[2] Dexketoprofen is the active enantiomer of racemic Ketoprofen and is responsible for all of the Cox-1 and Cox-2 inhibitory activity of ketoprofen.
[3] Dexketoprofen is therapeutically more effective even at half the dose of Ketoprofen in the treatment of pain caused due to dental extraction.
[4] Dexketoprofen 25mg is as effective as Ketoprofen 50mg in relieving the pain of dysmenorrhoea.
[5] Both Dexketoprofen and Ketoprofen are equally safe in Indian patients for these two indication

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Introduction

Racemic ketoprofen is a 50:50 mixture of S(+)- and R(-)-enantiomer [1]. Most or all COX inhibitory activity of ketoprofen is attributed to the S(+)-enantiomer (dexketoprofen) [2]. Dexketoprofen is a dual and fairly balanced inhibitor of cyclooxygenase (COX)-1 and COX-2 isoenzymes [3],[4],[5]. The R(-)-enantiomer is 30 to 5000 times less potent as an inhibitor of COX-1 and about 100 times less potent as an inhibitor of COX-2 [3]. Dexketoprofen has been shown to be effective in the symptomatic treatment of pain of mild to moderate intensity [6], such as musculo-skeletal pain [7],[8], dysmenorrhoea [9], dental pain [10],[11] and osteoarthritis [12],[13],[14].

In a study of clinical comparison of dexketoprofen trometamol, ketoprofen, and placebo in postoperative dental pain [11], the results showed that dexketoprofen trometamol 25 mg is at least as effective as the racemic ketoprofen 50 mg in the treatment of post surgical dental pain. Dexketoprofen trometamol also had a faster onset of action as compared to ketoprofen.

In another study [9], Dexketoprofen in the doses of 12.5 mg and 25 mg was significantly superior to placebo and as effective as Ketoprofen 50 mg in relieving pain due to Dysmenorrhoea. The safety profile was comparable with all the three doses of the study medications.

Present two studies were designed to assess the efficacy and safety of Dexketoprofen trometamol in the treatment of postoperative pain after dental procedure and in the treatment of dysmenorrhoea in Indian patients.

Materials And Methods

The dental pain study was conducted by four dental surgeons in India, in their respective out patient departments. A total of 50 patients were enrolled. The study was a multicentric, randomized, parallel group, comparative clinical trial. Male or female patients between 18-65 years of age, undergoing oral surgery consisting of extraction of the impacted or semi-impacted third molars and willing to give written informed consent and willing to comply with trial protocol were included.

The dysmenorrhoea study was conducted by three Gynaecologists in three different towns of India in their respective clinics/ nursing homes, on an out patient basis. Female patients in the age group 18 to 45 years, who were having painful menstruation and in whom empiric NSAID therapy was indicated with the presumptive diagnosis of primary dysmenorrhea, based on a typical history of low anterior pelvic pain beginning in adolescence and associated specifically with menstrual periods were enrolled in the study after obtaining written informed consent. Patients with hypersensitivity and/or contraindications to Ketoprofen or other NSAIDs were not included in the trial. Also patients with a history of peptic ulcers, patients who were required to take other NSAIDs/narcotic analgesics other than study medication, patients with impaired hepatic and/or renal function and patients who were deemed ineligible for any other reason, were excluded from the study. Patients who had taken any other analgesic in the past 24 hours were excluded as were pregnant and lactating women.

Interventions

Both the studies were comparative studies. Patients received treatment with either Dexketoprofen (from Emcure Pharmaceuticals Limited, India) 25mg one tablet TID or Ketoprofen (from Teva Pharmaceuticals, USA) 50mg one Capsule TID, as per randomization schedule. Randomization was done in 5 blocks of 10, as per the computer generated randomization chart (www.randomization.com). Each patient was dispensed a separate sachet containing the study medications adequate for the entire study duration.

The test (Dexketoprofen) and reference (Ketoprofen) medications were provided in

coated opaque sachets to conceal the identity of the treatment allocated from the investigator and the patient. The medication sachets were numbered as per the randomization chart. Patients were randomly allocated to the test or reference groups and given random numbers by a study coordinator, who also dispensed the medication sachets with matching random numbers. The random code was unknown to the investigators and patients and was broken after the study was over. Follow-up was ensured by providing clear instructions to patients regarding their visit schedule. Patients were also given patient information sheet to retain with them containing instructions regarding follow-up schedule and frequency.

For the dental pain trial, the patients with impacted or semi-impacted third molar tooth were screened for eligibility and willingness to participate in the study before being included. The dental extraction was performed using standard orthodox procedure for extraction of impacted/semi-impacted third molar. After 2 hours of surgery, the patients were administered the study medication after marking the baseline pain intensity on the visual analogue scale (VAS). The remaining doses were taken by the patients three times a day for three days. At the follow up visit after 3 days of therapy, the patient submitted the marked VAS to the investigator.

Patients with dysmenorrhoea were also randomized into similar two groups but the treatment duration was for 5 days. The patients marked the baseline pain intensity before taking the study medication and thereafter at pre specified intervals. The follow up visit was on the 2nd day and 5th day of therapy.

Efficacy

The dental pain patients were assessed at baseline (at two hours after surgery) and asked to mark the pain intensity on the VAS. The VAS was 100 mm long with 0 = no pain and 100 = maximal pain imaginable. The first dose was then administered. Patients marked the pain intensity on the VAS after 1 hour, 6 hours, and 8 hours of therapy and also on the 2nd and 3rd day. At the follow up visit, the patient diary card with the marked VAS was collected back.

In case of Dysmenorrhoea, baseline pain intensity was recorded on the VAS before administration of the study medication and after the 1st, 2nd and 3rd dose and also on the 2nd, 3rd, 4th and 5th day. At the last follow up visit the patient submitted the marked patient diary card.

The VAS severity score was then quantified by the investigators and recorded in the case record form (CRF). The onset of action (defined as the time required after administration of drug when patient experiences even a slight decrease in pain intensity) and the duration of action (defined as the time after administration of the drug for which the pain intensity remains decreased) were also recorded in the CRF by the physician.

Tolerability

At each follow up visit, any adverse event was inquired into and recording made accordingly. Need for any rescue analgesic was also inquired into each time patients were assessed during the study.

Ethics

The study was conducted in compliance with the ICH GCP regulations and in accordance with the Declaration of Helsinki of 1975 that was revised in 2000 and after each investigator was authorized by the local Ethics Committee. All patients in both the studies provided written informed consent.

Statistics

Standard descriptive analysis including mean and standard deviation (SD) are used for variables such as the height, weight and age. The paired t-test was performed to assess the significance of change in the VAS score from base line as well as between groups efficacy. The significance of the patients' and doctors' assessment of the

study medication was done using the Chi-square test. For all statistical analyses, p-value <0.05 was considered as statistically significant. Statistical analysis for the efficacy and safety variables was done using the GraphPad InStat software.

Results

Fifty (50) patients were enrolled and also completed the dental pain study. Twenty five patients received Dexketoprofen trometamol 25 mg tablets (1 tablet TID orally) and twenty five received Ketoprofen 50 mg capsules (1 capsule TID orally). There was no significant difference in the baseline characteristics of the two groups of patients (p>0.05) [Table/Fig 1]. There was no significant difference in the interventions performed or the antibiotic cover provided after the surgery. In both the groups comparable numbers received either of the four drugs/ drug combinations: Ciprofloxacin, Cefadroxil, Ofloxacin+ Ornidazole or Cefuroxime. There was a statistically significant (p=0.01) improvement in the VAS mean scores for symptoms of pain in the dexketoprofen group after 1 hour as well as 6 hours of administration of first dose whereas in the ketoprofen group, a significant decrease in pain intensity on the visual analogue scale score was observed only after 8 hours of drug administration [Table/Fig 2]. Thus dexketoprofen has shown faster onset of significant analgesia as compared to ketoprofen. The comparative difference between the two groups for VAS scores of pain was not statistically significant (p>0.05) at baseline and at 1 hour, 6 hours and at 8 hours after drug administration [Table/Fig 2]. However further analysis of the VAS score showed that patients in the dexketoprofen group experienced significantly higher analgesia on the first, second and third days of therapy as compared to the ketoprofen group [Table/Fig 2].There was no significant difference in the onset of analgesia between the two groups, 31.04 ± 24.99 mins for the Dexketoprofen group and 29.32 ± 21.89 mins for the Ketoprofen group (p=0.65). The duration of analgesia was 7.88 ± 3.21 hours and 6.98 ± 3.17 hours (p=0.06) for the Dexketoprofen and the Ketoprofen groups respectively.

In the Dysmenorrhoea study,fifty five (55) patients were enrolled and also completed the study. Twenty eight patients received Dexketoprofen trometamol 25 mg tablets (1 tablet TID orally). Twenty seven received Ketoprofen 50 mg capsules (1 capsule TID orally).There was no significant difference in the baseline characteristics of the two groups of patients (p>0.05) [Table/Fig 3].There was a statistically significant (p<0.01) improvement in the VAS mean scores for symptoms of pain in each group after first dose of the study drugs and also after the second dose, third dose and at 2^{nd}, 3^{rd}, 4^{th} and 5^{th} day of therapy as compared to baseline (before therapy) values [Table/Fig 4]. The comparative difference between the two groups for VAS scores of pain was not statistically significant (p>0.05) [Table/Fig 4]. The onset of analgesia was 22.68 ± 9.38 mins and 22.96 ± 7.88 mins (p>0.05) for the Dexketoprofen and Ketoprofen groups respectively.

None of the groups in both the studies required any rescue analgesic. None of the patients in either group in both the studies reported any side-effects and both the drugs were well-tolerated. There was no significant difference in the opinion of the patients as well as the investigators regarding the efficacy of either drug.

(Table/Fig 1)Baseline characteristics of patients with dental pain(n = 50)

		Dexketoprofen (25mg)	Ketoprofen (50mg)	p value
Total number of patients enrolled, n=		25	25	NA
Total number of patients who completed study, n=		25	25	NA
Age (yrs, mean ± SD)		34.24 ± 12.46	33.68 ± 10.00	NS
Sex	Male, n=	10	10	NS
	Female, n=	15	15	NS
Height (cm, mean ±SD)		157.96 ± 23.66	162.04 ± 9.01	NS
Weight (Kg, mean ± SD)		63.48 ± 9.98	60.82 ± 9.76	NS
Heart rate (per minute, mean ±SD)		75.64 ± 7.06	76 ± 6	NS
Systolic blood pressure, SBP (mmHg, mean ± SD)		119.64 ± 6.10	120 ± 6	NS
Diastolic blood pressure, DBP (mmHg, mean ± SD)		79.68 ± 4.96	80 ± 6	NS
Anemia		0	1	NA

NA: Not applicable; NS = p > 0.05

(Table/Fig 2). Dental pain Intensity on Visual Analogue Scale (values expressed as mean ± SD)

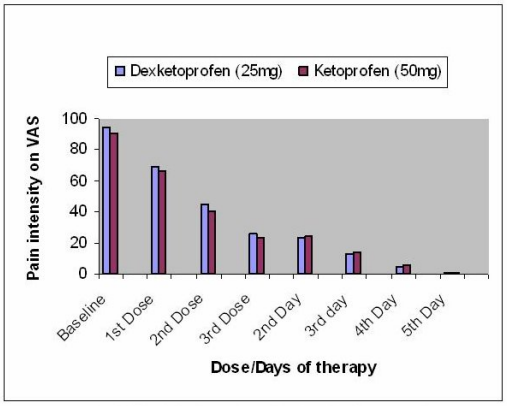
	Dexketoprofen (25mg)	Ketoprofen (50mg)	p value		
			Between groups	Vs Baseline	
				Dexketoprofen	Ketoprofen
Baseline*	51.12 ± 23.56	46.28 ± 25.77	NS	NA	NA
At 1 hour#	36.92 ± 15.91	39.76 ± 23.53	NS	P=0.0160	P= 0.3549
At 6 hours	27.96 ± 14.00	34.16 ± 24.61	NS	P=0.0001	P=0.0955
At 8 hours	24.16 ± 12.52	28.36 ± 22.82	NS	P<0.0001	P<0.0001
1st Day	12.44 ± 11.80	25.84 ± 23.45	0.02	P<0.0001	P<0.0001
2nd Day	9.72 ± 13.30	20.80 ± 17.97	0.02	P<0.0001	P<0.0001
3rd Day	10.12 ± 13.41	15.20 ± 15.03	0.22	P<0.0001	P<0.0001

*Baseline=after 2 hours of surgery or when patient experiences pain whichever is earlier.
#After 1 hour of drug administration.
NA=Not applicable; NS=Not Significant

(Table/Fig 3) Baseline characteristics of patients with dysmenorrhoea (n = 55)

		Dexketoprofen (25mg)	Ketoprofen (50mg)	p value
Total number of patients enrolled, n=		28	27	NA
Total number of patients who completed study, n=		28	27	NA
Age (yrs, mean ± SD)		27.2 ± 6.36	25.8 ± 6.2	NS
Height (cm, mean ±SD)		157.68 ± 10.63	155.8 ± 7.99	NS
Weight (Kg, mean ± SD)		54.52 ± 10.67	50.29 ± 6.82	NS
Heart rate (per minute, mean ±SD)		80.2 ± 4.72	80.8 ± 4.1	NS
SBP (mmHg, mean ± SD)		115.86 ± 7.14	116.22 ± 5.85	NS
DBP (mmHg, mean ± SD)		76.79 ± 5.31	76.0± 5.11	NS
Anemia		03	01	NA
Length of Menstrual Cycle		4.37 ± 1.1	4.5 ± 1.1	NS
Menstrual Cycle	Regular, n=	23	22	NS
	Irregular, n=	05	05	NS
Type of Dysmenorrhoea	Congestive, n=	13	13	NS
	Spasmodic, n=	15	14	NS
Significant past history		Appendicectomy , n=1	0	NA
Concomitant Medications		Ofloxacin +Ornidazole, n=1	Fluconazole, n=1	NA

NA: Not applicable; NS = p > 0.05



(Table/Fig 4) Efficacy in patients with dysmenorrhea

Conclusion

The results of this multi-centric, randomized, comparative clinical trial to evaluate the efficacy and safety of Dexketoprofen trometamol 25 mg versus Ketoprofen 50 mg in the treatment of pain due to dental surgery shows that Dexketoprofen trometamol 25 mg is equally effective as compared to Ketoprofen 50 mg in decreasing pain due to dental extraction in the first 8 hours of therapy. Dexketoprofen has a better analgesic effect at 24 hours and on the second and third day of therapy as compared to Ketoprofen. Dexketoprofen provided significant analgesia within 1 hour of dosing whereas though Ketoprofen decreased the pain intensity at 1 hour, statistically significant analgesia was observed only after 8 hours of therapy with ketoprofen. Both the drugs have similar onset and duration of action and are safe and well-tolerated in this indication.

In case of dysmenorrhoea, Dexketoprofen (25 mg) and Ketoprofen (50 mg) showed equal efficacy in relieving pain and both the drugs were very well tolerated by Indian patients.

Discussion

Various clinical trials have demonstrated that Dexketoprofen, the S (+) enantiomer of Ketoprofen, is a quick acting analgesic for the treatment of painful musculoskeletal conditions such as osteoarthritis and low back pain and has also demonstrated favourable efficacy and tolerability profile

in the treatment for post-operative pain, toothache and dysmenorrhoea [15].

Our study in Dental pain showed that both Dexketoprofen and Ketoprofen were effective analgesics in post surgical dental pain and significant analgesia was achieved faster with Dexketoprofen than with Ketoprofen. These findings are consistent with the findings of McGurk M et al [11] who concluded that the rapid onset of action of Dexketoprofen trometamol as compared to Ketoprofen makes it a more suitable analgesic for treatment of acute pain.

Our findings in the Dysmenorrhoea study are consistent with the findings of Ezcurdia M et al [9] that Dexketoprofen at half the dose provides analgesia comparable to full dose of racemic Ketoprofen.

For both the indications both the drugs were safe and very well tolerated.

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