Original Article

Evaluation of the Effectiveness and Safety of a New Formulation of Injection Diclofenac DYNAPAR AQ (75mg/ml) in the Management of Post-operative Pain — A Pilot Study

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Abstract

Introduction

DYNAPAR AQ, a new formulation of diclofenac sodium suitable for intradeltoid injection was developed. The aim of the study was to evaluate the efficacy and safety of intradeltoid DYNAPAR AQ in the management of post-operative pain.

Methods

191 adult patients with post-operative pain [VAS (Visual Analogue Scale) greater than or equal to 7] received a single dose of DYNAPAR AQ injected intradeltoid. Primary efficacy criteria were time to onset of analgesia and reduction in pain intensity. Pain intensity was recorded at 1, 4, 8 and 12 hours. Severity of pain at site of injection was recorded at 1 and 12 hours.

Results

Following administration of DYNAPAR AQ mean pain intensity fell significantly by 37.6, 56.5, 61.0 and 62.8 percentage at the end of 1, 4, 8 and 12 hours respectively (p less than 0.05 for all time points as compared to baseline). Mean time taken for onset of analgesia was 20.37 plus or minus 10.22 minutes. 18 of the 191 patients needed rescue analgesia. Most patients experienced either no pain or mild pain at site of injection. There was no report of severe pain.

Conclusion

Intradeltoid DYNAPAR AQ appears to be efficacious and well tolerated in the management of post-operative pain. This would especially be helpful in the management of patients with thick subcutaneous fat in the gluteal region.

Keywords

Injection diclofenac, intradeltoid, new formulation

Introduction

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) advocated for use in painful and inflammatory

rheumatic and certain non-rheumatic conditions[10]. It can be given orally, rectally, intramuscularly or as intravenous infusion. Diclofenac has exhibited effective pain control after herniotomy, orchidopexy, or minor gynaecological surgery[1,2]. Intramuscular administration of diclofenac has been shown efficacious for pain reduction following a variety of surgeries - hip, abdominal, dental, laparoscopy, ENT[5,6,9,13,14]. Extensive clinical experience has been gained with diclofenac, clearly establishing its safety profile. It is well tolerated compared with other NSAIDs and rarely produces gastrointestinal ulceration or other serious side effects. Thus, diclofenac can be considered as one of the few NSAIDs of 'first choice' in the treatment of acute and chronic painful and inflammatory conditions[10].

Intramuscular injections of diclofenac are commonly used in the management of post-operative pain. Due to its large injection volume (3ml) diclofenac injections are currently administered deep intramuscularly, generally intragluteally.

For optimal effect following an intramuscular injection it is important that the drug be delivered to the muscle. Problems can arise if drugs designed to be absorbed from muscle are only delivered into subcutaneous tissue. Increasing obesity in all developed and many developing countries make this an increasing concern.[15] Other injection sites like the deltoid could be more suitable for these patients. This site has the advantage of being easily accessible whether the patient is standing, sitting or lying down. Owing to the small area of this site, the number and volume of injections which can be given into it are limited. The currently available formulation of injection diclofenac precludes an intradeltoid injection due to its larger injection volume.

DYNAPAR AQ a new formulation of injection diclofenac has recently become available for clinical use in India. It provides 75 mg of diclofenac in one ml solution. By virtue of its small volume it can be given intradeltoid.

The present study is a pilot study to determine the effectiveness and safety of a single dose of DYNAPAR AQ administered intradeltoid in the management of post-operative pain in patients undergoing elective surgery.

Methods

The study was carried out at 4 institutes across India. The protocol was approved by the individual Ethics Committee of all 4 institutes.

After the individual institutional ethics committee approvals and written informed consent from the participants in the study, 196 adult (18-60 years) patients of ASA (American Society of Anesthesiology) grade I and II, of either sex undergoing elective general surgical or orthopedic procedures with severe post-operative pain VAS (Visual Analogue Scale) 7 or more were enrolled for the study. Exclusion criteria included out-patients, patients with known hypersensitivity or contra-indications for diclofenac/ NSAIDs (non- steroidal anti- inflammatory drugs). Patients who were not willing to or unable to give consent were not included in the study.

Since this was a pilot study to evaluate the efficacy and safety of a new formulation of injection diclofenac, it was designed as an open label, non-comparative study.

Post-operatively patients received a single 75 mg dose of DYNAPAR AQ (Injection diclofenac sodium 75mg/ ml, manufactured by Troikaa Pharmaceuticals Limited, Ahmedabad, India) intradeltoid using 24 gauze needle. Method for injection has been described earlier[7]. Patients were explained that they could ask for rescue medications for pain, if needed. Injection Tramadol 50 mg was given, if required by the patient.

Pain intensity was measured with a 0-10 point VAS, 0 representing no pain and 10 worst possible pain. The VAS recording immediately prior to administration of study medication served as baseline pain intensity score. VAS was recorded at 1, 4, 8 and 12 hours after the administration of the test medication. At each observation time point, all patients were ascertained about side effects. If present, type and severity of the event was recorded. Severity of pain at site of injection as determined by VAS was recorded at 1 and 12 hours following the injection.

Efficacy criteria were time to onset of analgesia and VAS at 1 hour and 12 hours. Safety was determined by monitoring adverse events and pain at site of injection.

Statistics

All data were expressed in terms of mean ± SD (standard deviation). Wilcoxon Sign Rank Test was applied to determine the significance of differences between two

readings and between baseline and end of study. A p-value of less than 0.05 was regarded as significant.

The sample size was calculated using a level of significance of 5%, power of 87% and critical evaluable difference of 10% based on studies with 3 ml formulations of injection diclofenac.

Results

Of the 196 eligible patients enrolled in the study there were 5 drop outs due to protocol violation, hence only 191 patients were available for efficacy and safety analysis. This included 97 patients undergoing orthopedic procedures and 84 patients undergoing various major general surgeries **(Table 1).**

Table 1
Demographic data of analyzable patients

Number of patients		
	Enrolled	196
	Drop outs	5
	Analyzable	191
Age (years)		
	Mean	39.69 ± 13.27
	Range	18- 60
Weight (Kg)		
	Mean	62.57 ± 10.90
	Range	50-92 kg
Sex [no (%)]		
	Male	127 (66.5)
	Female	64 (33.5)
Type of Surgical Procedures		
	General Surgical	84
	Orthopedic	97

Baseline VAS score was 8.65 ± 1.01 **(Table 2).** After administration of DYNAPAR AQ at the end of 1 hour the mean VAS score fell significantly by 37.6% ($p < 0.05$). At the end of 4 hours the fall was 56.5%. At the end of 8 and 12 hours fall was 61.0% and 62.8% respectively from basal ($p < 0.05$). The change in mean VAS score was similar across all types of surgeries.

The mean time taken for onset of analgesia was 20.37 ± 10.22 minutes. Only 18 of the 191 patients needed rescue analgesia. Of the 191 patients 74 patients experienced no pain at site of injection, 63 complained of mild pain (VAS ≤ 3) and 54 patients experienced moderate pain (VAS 4 to 6). No patient complained of severe pain. There were 6 complaints of nausea and vomiting and 2 complaints of headache.

Table 2
VAS score at different time points during the study period

Observation point (hours from baseline)	Mean VAS Score (Mean ± SD)
Baseline	8.65 ± 1.01
1	*5.40 ± 1.89
4	*3.76 ± 1.86
8	*3.37 ± 1.18
12	*3.22 ± 1.35

*p less than 0.05 as compared to baseline

A retrospective power of analysis confirmed the power of 86.32%.

Discussion

Intramuscular injections of diclofenac are commonly used in the management of post-operative pain. Currently available formulations of injection are administered deep intramuscularly, generally intragluteal. Problems can arise if drugs designed to be absorbed from muscle are only delivered into subcutaneous tissue. Increasing obesity in developed and many developing countries make this an increasing concern.

Achieving true intramuscular injection is determined by both the injection technique and the needle size. Although standard fixed needles are perceived as being more convenient to use they may fail to deliver intramuscular medications reliably in all cases, since the body mass index of patients varies considerably[16].

In a prospective study on inpatients undergoing computerized tomography Chan OV *et al* 2006, observed that overall, only 32% of patients prescribed intramuscular medications had intramuscular injections, with the majority

of injections (68%) being subcutaneous. When analyzed by gender, 56% of males had intramuscular injections while in females, the efficacy rate was significantly lower at 8%. Thus, the majority of assumed intramuscular injections are actually subcutaneous[4]. Nisbet AC 2006 also reported that standard needles do not reach the gluteal muscles in a considerable number of patients[8]. Based on the measurement of gluteal region subcutaneous fat thickness performed for 298 pelvic CT scans, Burbridge 2007, predicted an overall failure rate of 34% for intended gluteal intramuscular injections when the standard technique was used. In a significant number of patients, the medications were injected subcutaneously and not into the gluteal musculature, possibly altering the pharmacokinetics of the administered medication. They concluded that an alternative injection site should probably be chosen to increase the success rate of intramuscular deposition of medications and vaccines in unselected adults[3].

Alternative sites for intramuscular injections like the deltoid have been suggested. The efficacy and safety of a new 75mg/ 1ml formulation of injection diclofenac injected intradeltoid was evaluated in the management of post operative pain in patients undergoing elective surgery. The mean time to onset of analgesia of about 20 minutes was similar to earlier reports with conventional diclofenac injections[12]. A significant reduction in VAS score was seen at 1 hour post-injection. The VAS fell from a baseline of 8.65 ± 1.01 to 5.40 ± 1.89 at 1 hour. Analgesia was well maintained up to 12 hours. Significant reductions at 1 hour have also been reported by earlier workers with conventional diclofenac injections[1]. The new formulation was also well tolerated. No abnormalities in routine haemodynamic parameters observed till the end of study.

Although upper mid-arm circumferences were measured to provide uniformity of the subcutaneous fat in deltoid region, this may not be actually required. It has been reported that needles of 1 inch length would penetrate the deltoid area in men weighing 59-118 kg and women weighing up to 90 kg[11].

Despite the limitations of the study design the new formulation of injection diclofenac (75mg/ml) appears to be efficacious and well tolerated in the management of post- operative pain. Injection diclofenac can now be given at alternative site like the deltoid. This would especially be helpful in the management of obese patients and patients with a thick subcutaneous fat in the gluteal region. However, this need to be confirmed by randomized double blind comparative studies.

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