

DICLOFENAC 75MG/1ML INTRADELTOID INJECTION FOR POST OPERATIVE PAIN MANAGEMENT IN PATIENTS WITH BMI \geq 25 KG/M²

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ABSTRACT

BACKGROUND: Diclofenac 75mg/3ml intragluteal injection is currently used for postoperative pain management. Studies have shown that standard needles do not reach gluteal muscles of patients with Body Mass Index (BMI) \geq 25 kg/m². Also, larger volume for injection causes more muscle damage as compared to lesser volumes. Objective of this study was to compare safety and efficacy of diclofenac 75mg/1ml intradeltoid injection versus diclofenac 75mg/3ml intragluteal injection for postoperative pain management in patients with BMI \geq 25 kg/m². **MATERIALS AND METHODS:** In this active controlled, multicentric study, enrolled subjects (n=189) were randomized to receive either Diclofenac 75mg/1ml intradeltoid injection or Diclofenac 75mg/3ml intragluteal injection. Study drugs were administered at 0 (baseline), 12, 24 and 36 hours. Time to onset of analgesia, postoperative pain intensity, degree of pain relief, pain at site of injection, local reactions or any other adverse events were recorded upto 12 hr after each dose over 48 hour study period. Global assessment of treatment was also recorded at end of study. **RESULTS AND DISCUSSION:** Both the study drugs were comparable in terms of degree of pain relief. Significantly faster onset of analgesia ($p < 0.0001$); lesser intensity of pain at site of injection [$p < 0.0046$ at 1 hr and ($p < 0.0001$) at 12 hr] and lesser incidence of local reactions at the site of injection were observed with diclofenac 75mg/1ml intradeltoid injection. Global assessment of treatment was favorable for diclofenac 75mg/1ml intradeltoid injection. **CONCLUSION:** Diclofenac 75mg/1ml intradeltoid injection can be a better alternative for post operative pain management in patients with BMI \geq 25 Kg/m².

Keywords: Diclofenac, intramuscular, postoperative pain, Body Mass Index, pain management

INTRODUCTION

Post-operative pain is one of the most common forms of acute pain¹ and may be associated with delayed healing, longer hospitalization and the development of chronic pain. These results in increased suffering and cost of therapy.^{1,2} Adequate pain management in postoperative patients contributes to earlier mobilization, shorter hospital stay and lower costs.² Post operative pain is mainly due to inflammation combined with primary repair, thus Non Steroidal

Anti-Inflammatory Drugs (NSAIDs) are effective analgesics in this condition as they block the source of pain. Diclofenac sodium is one of the most commonly used and effective NSAID in the management of postoperative pain.^{3,4,5} Conventional diclofenac injections are available in 3 ml volume to deliver 75 mg. Due to 3 ml volume; the injection needs to be given over the gluteal region. The novel diclofenac injection Dynapar AQ 1ml contains 75 mg diclofenac in 1 ml. Due to lesser volume it can be administered into deltoid muscles. Intradeltoid route has advantage of better blood flow, leading to increased absorption and faster onset of action. Further it does not require change of needle length in patients with higher BMI as the standard needle reaches the deltoid muscle. Intra deltoid route may be more convenient to patients also as they need not to move to expose the gluteal region as well it avoids exposure of the part and embarrassment associated with it.⁶ Intragluteal route of drug administration may be difficult in post operative, bed ridden patients in whom movements are

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restricted and painful. Intradeltoid is the preferred route of intramuscular drug administration especially in patients with Body Mass Index (BMI) ≥ 25 kg/m². Various studies have shown that standard size needles fail to reach and deliver the medicine in the gluteal muscle due to thick layer of subcutaneous fat, especially in obese patients.^{7,8,9} Troikaa Pharmaceuticals Ltd, Ahmedabad, India has developed a new formulation of diclofenac containing 75 mg in 1 ml (Dynapar AQ). One ml volume to administer desired therapeutic dose makes it possible to be injected in the deltoid muscle. Moreover, lesser volume of drug will cause relatively less muscle damage leading to lesser pain at site of injection.^{10,11} A pharmacokinetic study of Dynapar AQ intradeltoid injection versus diclofenac 75mg/3ml intragluteal injection was conducted in healthy Indian volunteers with BMI ≥ 25 kg/m². The results of this study showed that both the study drugs had comparable bioavailability; however, earlier time to reach maximum plasma concentration (T_{max}) and a trend towards a higher maximum plasma concentration (C_{max}) was noted with Dynapar AQ intradeltoid injection.¹² Based on these facts, we hypothesized that the diclofenac 75mg/1ml formulation for intradeltoid injection would produce early onset of analgesic action in patients with BMI ≥ 25 kg/m². We also hypothesized that diclofenac 75mg/1ml injection would produce lesser pain at the site of injection due to its reduced volume of therapeutic dose administration. Objective of this study was to compare safety and efficacy of diclofenac 75mg/1ml intradeltoid injection versus diclofenac 75mg/3ml intragluteal injection for postoperative pain management in patients with BMI ≥ 25 kg/m².

MATERIALS AND METHODS

A prospective, randomized, parallel, open label, comparative, active controlled, multicentric clinical study was conducted at two study centres in India. From January 2009 to June 2010, 200 patients of either sex of 18-65 years, undergoing elective surgeries such as orthopaedic, abdominal, gynaecological, otolaryngological and those requiring hospitalization for at least 48 hours post-operatively were enrolled. Exclusion criteria included out-patients, patients with BMI less than 25 kg/m², known hypersensitivity or contraindications for diclofenac/NSAIDs, patients with compromised renal function, history of bronchial asthma, peptic ulceration, bronchitis, coagulation disorders and mentally retarded patients. Women of child bearing age underwent the urine pregnancy test; pregnant and lactating women were excluded in the present study. During the screening visit on the day before surgery, medical history was obtained; physical examination and laboratory

investigations were performed. Medications considered necessary for the patient and which does not interact with the study medication were allowed. All patients were explained the procedure clearly and written informed consent from each participant was obtained before their participation in the study. The protocol was approved by respective Ethics Committees. The study was conducted in compliance with the Ethical principles of Declaration of Helsinki; Good Clinical Practices guidelines issued by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, Government of India; Ethical guidelines for biomedical research on human participants, Indian Council of Medical Research (ICMR), New Delhi; and International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use – guideline for Good Clinical Practices. The trial was registered with Clinical Trial Registry-India (CTRI) under registration number: CTRI/2009/091/000108 before initiation of study at the study centres. The trial was conducted at Hardikar Hospital, Pune and CSM Medical University, Lucknow over the duration of January 2009 to June 2010. Enrolled subjects were divided into two groups as per computer generated randomization sheet. One group (Group A) received diclofenac 75mg/1ml (Dynapar AQ, manufactured by Troikaa Pharmaceuticals Ltd, Ahmedabad, India) intramuscularly into the deltoid muscle and other group (group B) received diclofenac 75mg/3ml deep intramuscularly into gluteal muscle. Type of surgery, duration of surgery, use of Tramadol, and use of epidural anaesthesia in both the treatment groups was recorded in the case record form of each patient. *Study Parameters* Both the study drugs were administered post-operatively when the patient felt moderate to severe intensity of post operative pain; on a Visual Analogue Scale (VAS) score of 4-10 after recovery from the anaesthesia. The scale had a rating from 0-10 with “0” indicating no pain and “10” worst possible pain. Both the study drugs were administered after assessment of VAS score at 0 hour (baseline), 12 hour, 24 hour and 36 hour (total of 4 doses of each study drug). Safety and efficacy of both the formulations was evaluated over study period of 48 hours. Injections were given in left and right side of deltoid and gluteal region alternatively using 2cc or 5cc syringe and 24 gauge needles, under aseptic precautions by the health personnel. Following administration of each dose of study drugs, the time to onset of analgesia was assessed from each patient. Intensity of post operative pain was assessed by using VAS at 0 (predose), 1, 4, 8 and 12 hours after each dose. Pain relief (degree of analgesia) was assessed at 1, 4, 8 and 12 hours after

each dose using a 5- point scale (0- No Pain Relief, 1- Mild Pain Relief, 2- Moderate Pain Relief, 3- Good Pain Relief, and 4- No Pain).¹³ Pain at the site of injection was also assessed at the end of 1 and 12 hours after each dose with the help of VAS. Local reactions at the site of injection, adverse events or side effects observed during study period were also recorded. If no pain relief was observed (VAS score > 4) after 30 minutes of injecting the study medications, intravenous injection of tramadol 50 mg was to be used as the rescue medication. At the end of study period, global assessment of treatment based on efficacy and tolerability was assessed from physicians and patients. Based on the study of diclofenac intradeltoid injection in patients with post-operative pain¹⁴, standard deviation (SD) of 11.79 was taken for time to onset of analgesia. To detect clinically relevant difference of 5 minutes in time to onset of analgesia between two groups, the sample size calculated at 80% power and at 5% level of significance using two sided test, was 88 patients in each group to draw the conclusion. Considering a dropout rate of 10%, 197 patients would be required in the 2 groups. Based on this sample size of 200 subjects was considered for this study. Sample size calculation was performed using software, PS Power and Sample Size Calculations Program, version no.3. All statistical analyses were performed on an intention-to-treat basis. All statistical analyses were performed using software, GraphPad prism, version no.5. *P* value of less than 0.05 was considered as significant.

RESULTS

Out of 200 patients enrolled, total of 189 patients successfully completed study. Baseline variables (age, gender, BMI, type of surgery, duration of surgery, baseline pain intensity, use of epidural anesthesia and use of Tramadol were comparable among both the treatment groups (Table 1). The mean time to onset of analgesia was significantly less($p < 0.0001$) in diclofenac 75mg/1ml intradeltoid

Table 1: Patients baseline characteristics

Baseline characteristic	Diclofenac 75mg/1ml (N = 97)	Diclofenac 75mg/3ml (N = 92)	p value
Age (Year)	43.38±12.39	44.84±12.48	0.422*
Gender (Male/Female)	44/53	48/44	0.38**

Body Mass Index (BMI) (Kg/m ²)	28.86 ± 4.10	28.02 ± 3.28	0.12*
Type of surgery			
Orthopaedic	53	51	0.68**
Gynaecological	14	10	
Otolaryngological	10	7	
General surgery	20	24	
Duration of surgery (in minutes)	85.46±40.07	88.15±39.0	0.641*
Baseline Pain Intensity (VAS score)	7.30 ± 2.14	7.31 ± 2.15	0.95*
Use of epidural anesthesia (Yes/No)	8/89	7/85	0.87**
Use of Tramadol (Yes/No)	31/66	31/61	0.92**

Values are expressed in Mean ± SD for age, BMI, VAS (Visual Analogue Scale) score and duration of surgery; absolute number for gender, use of epidural anaesthesia, use of Tramadol and type of surgery; N = Number of subjects in treatment group. *Data was analyzed by unpaired 't' test **Data was analyzed by Chi square test

Figure 1: Showing the comparison of mean VAS score between the treatment groups. VAS score for post operative pain intensity decreased within each treatment group over a period of 48 hours from baseline. There was no stastically significant difference between the treatment groups ($p \geq 0.05$). Study drug was administered at 0 (baseline), 12, 24, and 36 hours (as indicated by arrow).

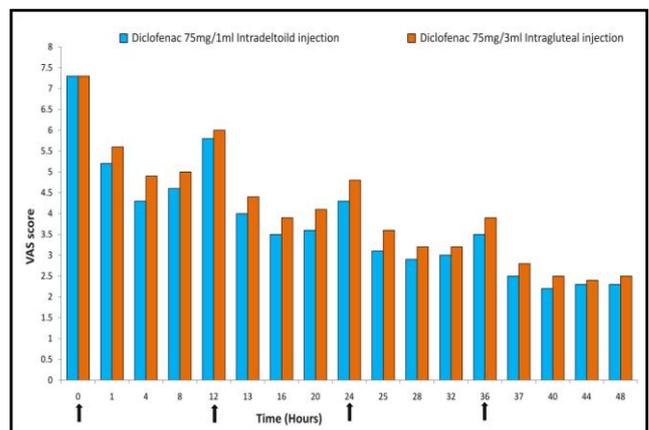


Table 2: Time to onset of analgesia

Drug administration	Time to onset of analgesia (minutes)		p value
	Diclofenac 75mg/1ml (N=97)	Diclofenac 75mg/3ml (N=92)	
1 st dose(0 hr)	18 ± 8.7	26 ± 15	< 0.0001
2 nd dose(12 hr)	16 ± 6.9	24 ± 9.6	< 0.0001
3 rd dose(24 hr)	15 ± 5.7	21 ± 9.3	< 0.0001
4 th dose(36 hr)	15 ± 5.2	19 ± 9.1	0.0006

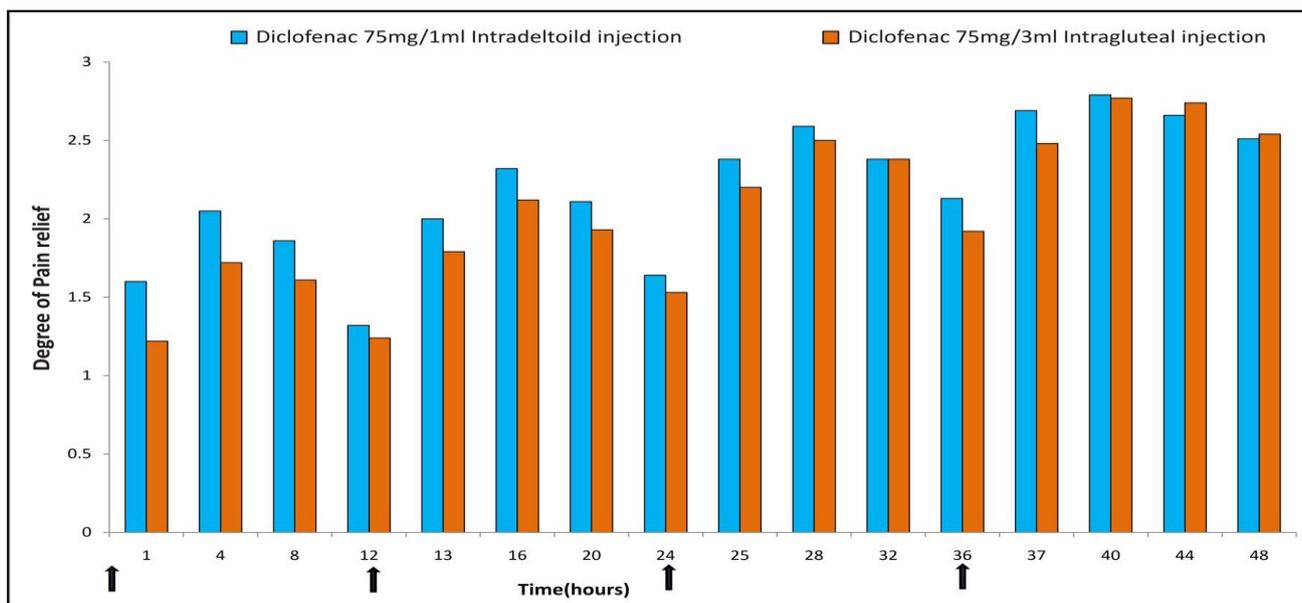
Values are expressed in Mean ± SD; N = Number of subjects in treatment group. Data was analyzed by unpaired ‘t’ test.

Table 3: Global assessment by patient and Investigator

Global Assessment	Patient’s global assessment		Investigator’s global assessment	
	Diclofenac 75mg/1ml (N=97)	Diclofenac 75mg/3ml (N=92)	Diclofenac 75mg/1ml (N=97)	Diclofenac 75mg/3ml (N=92)
Excellent	12	7	17	10
Good	71	57	69	48
Fair	14	26	11	32
Poor	0	2	0	2
p value	0.0398		0.0005	

N = Number of subjects in treatment group. Numerical represent number of subjects for particular assessment. Data was analyzed by Chi square test

Figure 2: Showing the comparison of mean degree of pain relief between the treatment groups. Improvement in degree of pain relief was observed within each group over a period of 48 hours from baseline. There was no stastically significant difference between the treatment groups (p≥ 0.05). Study drug was administered at 0 (baseline), 12, 24, and 36 hours (as indicated by arrow)



injection group as compared to the conventional, diclofenac 75mg/3 ml intragluteal injection group after administration of each dose of study drug

(Table 2). There was gradual reduction in intensity of post operative pain over a period of 48 hours in both the treatment groups as observed from the

reduction trend in the VAS scores from baseline. No statistically significant difference was observed between the treatment groups for intensity of post operative pain (Figure 1) and degree of pain relief over a period of 48 hrs (Figure 2). Intensity of pain at the site of injection after administration of diclofenac 75mg/1ml intradeltoid injection group was 1.6 ± 1.7 at 1 hour and 0.40 ± 0.97 at 12 hour respectively; and after administration of diclofenac 75mg/3ml intragluteal injection, was 1.9 ± 1.9 at 1 hour and 0.75 ± 1.1 at 12 hour respectively. Intensity of pain at the site of injection was significantly lesser in patients treated with diclofenac 75mg/1ml intradeltoid injection at 1 hour ($p < 0.0046$) and 12 hours ($p < 0.0001$) after all the doses of study drug administration. The local reactions (swelling, indurations and redness) at injection site were observed in 9 (9.2%) patients treated with diclofenac 75mg/1ml intradeltoid injection and 16 (17.4%) patients treated with diclofenac 75mg/3ml intragluteal injection. The patients' and Investigator' global assessment scores were significantly favorable for diclofenac 75mg/1ml intradeltoid injection (Table 3) No cases of any other expected or unexpected systemic adverse events were observed during the study period.

DISCUSSION

The present study explored the effect of diclofenac 75mg/1ml intradeltoid injection versus diclofenac 75mg/3 ml intragluteal injection, in patients with $BMI \geq 25 \text{ kg/m}^2$ for treatment of post operative pain using a comparative approach. The maximum volume of injection which can be injected in intradeltoid muscle is 2 ml, so the comparator was administered in to intragluteal muscles. Since the two groups were administered with different drug volumes at different sites of injection, the study was open-label. Study demonstrated that both the formulations of diclofenac were effective in the management of postoperative pain. However, the patients treated with diclofenac 75mg/1ml intradeltoid injection experienced significantly rapid onset of analgesia and lesser pain at the site of injection as compared to the patients treated with diclofenac 75 mg/3 ml intragluteal injection. Moreover, lesser number of patients in Dynapar AQ intradeltoid injection group experienced local adverse reactions as compared to diclofenac 75mg/3ml intragluteal injection. These results corroborated with similar findings of several other clinical studies. Numerous studies reveal that rapid onset of analgesia may be attributed to the faster rate of absorption after intramuscular injection given into the deltoid than that given into the gluteus maximus.^{10,15} Several evidences suggest that the deltoid is better site for intra muscular injection

than gluteal^{6,8,15,16} as it ensures the delivery of the drug in the muscle especially in obese individuals who have thick subcutaneous fat; and thus offers rapid onset of action. The reason for delay in onset of analgesia following intragluteal administration is also well documented in literature. Numerous studies have suggested that the standard needles do not reach the gluteal muscles in a significant number of obese patients because they have thick pad of fatty tissue between the skin and the muscle in their gluteal region.¹⁷ A radiological study conducted on 50 inpatients to determine whether intramuscular injections given into the buttocks are truly intramuscular; suggested that only 32% ($n=16/50$) of patients had intramuscular injections, with the majority of injections (68%, $n=34/50$) being subcutaneous, not into gluteal muscle. This results in alteration of pharmacokinetics of administered medication¹⁸ and increase in time to onset of action which could be the possible reason for delay in onset of analgesia of conventional formulation of diclofenac 75mg/3 ml injection. Our results presenting reduced pain at injection site, were consistent with the findings of Svendsen and colleagues, who have reported that a smaller volume of a concentrated solution causes less muscle damage than a larger volume of a relatively less concentrated solution.¹¹ Local reaction at the site of intragluteal injection may be due to more muscle damage following i.m. injection which is directly proportional to the volume of injected solution.¹¹ Comparing overall safety and efficacy of the study drugs, the patients' and investigator's assessment (in terms of global assessment) was significantly favorable for Dynapar AQ intradeltoid injection than diclofenac 75mg/3m lintragluteal injection. This may be because; the intradeltoid administration of Dynapar AQ injection offered significantly rapid onset of analgesia and better tolerability at the site of injection

CONCLUSION

Both the formulations of diclofenac injection were effective in post operative pain in patients with $BMI \geq 25 \text{ Kg/m}^2$. However, Dynapar AQ (diclofenac 75mg/1ml) intradeltoid injection was found to be associated with faster onset of analgesia, lesser pain at the injection site and convenience of intradeltoid administration. Hence, 1ml formulation of diclofenac 75mg for intradeltoid injection could be a better alternative in the management of post operative pain management in patients with $BMI \geq 25 \text{ Kg/m}^2$.

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