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DYNAPAR AQ IV BOLUS INJECTION FOR POSTOPERATIVE PAIN

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ABSTRACT:

Aim: To evaluate safety and efficacy of diclofenac 75 mg/1ml (Dynapar AQ) administered as IV bolus versus diclofenac 75mg/3ml administered as IV infusion in patients with postoperative pain.

Methods: 350 postoperative adult patients were randomized to receive either treatment. Primary efficacy endpoints were time to onset of analgesia and postoperative pain intensity while secondary efficacy endpoints included degree of pain relief and global assessment by patient and investigator. The safety endpoints were pain intensity and grade of thrombophlebitis at injection site. Safety and efficacy endpoints were evaluated over 12 hour study period.

Results: Both study drugs were safe and effective throughout study period. However, IV bolus route of Dynapar AQ produced significantly faster onset of analgesia, better improvement in postoperative pain intensity and pain relief upto 1 hour, lesser thrombophlebitis and lesser pain at administration site upto 8 hours. Also, global assessment by patient and investigator was significantly favorable towards Dynapar AQ.

Conclusions: IV bolus route of Dynapar AQ is better alternative to IV infusion of diclofenac 75mg/3ml with rapid onset of analgesia and better tolerability at injection site.

INTRODUCTION: Acute pain, such as moderate to severe post-operative pain, is normally managed with opioids or NSAIDs [1].

Opioid analgesics have long been the primary pharmacotherapy for moderate to severe pain after surgery, but are associated with number of adverse effects, such as respiratory depression, sedation, nausea and vomiting, pruritus, urinary retention and ileus [1, 2, 3].

Non-selective NSAIDs are effective analgesics and have been used instead of opioids, or adjunctively to reduce opioid consumption, with the aim of reducing opioid-related adverse effects.

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Parenteral formulations are often preferred when patients are unable to take oral medications, or require rapid onset of analgesia [4].

Diclofenac is an effective and well tolerated non-selective NSAID recommended for the treatment of acute painful and inflammatory conditions [5, 6]. In India, Injectable diclofenac formulations are approved for intramuscular use and also as an intravenous (IV) infusion in the management of post-operative pain. However, IV bolus route of diclofenac 75mg/2ml is approved in European countries for clinical use. Further, several lines of clinical evidence suggested that intravenous administration of diclofenac sodium 75mg is safe and well tolerated in the managing pain following surgery [7, 8]. Despite its proven efficacy and safety in the treatment of post-operative pain, the use of injectable diclofenac in India is restricted by the fact that current formulations have to be administered by either intramuscular injection or by slow intravenous infusion.

Due to the poor solubility of diclofenac, intravenous administration of 3ml formulation of diclofenac 75mg requires dilution with 100–500 ml of either sodium chloride solution (0.9%) or glucose solution (5%). Thereafter, it should be buffered with sodium bicarbonate solution, and infused continuously over a period of 30 minutes to 2 hours. This makes the administration complicated and time-consuming and is associated with costs due to the consumables, staff and time required to set up and monitor an intravenous infusion. The importance of dilution and buffering prior to administration is highlighted by the observation that IV administration of undiluted diclofenac is associated with an increased incidence of venous thrombosis close to the injection site which is attributed to the PG present in conventional formulations [7].

DYNAPAR AQ (Diclofenac 75mg/1ml), a reduced-volume PG free formulation of injection diclofenac has become available for clinical use in India by Troikaa Pharmaceutical limited. This formulation is compatible with common dilution fluids and it is being administered without the need of buffering. As this formulation does not contain PG it can be considered as a potential formulation for IV direct/ bolus use.

Based upon the above facts, we hypothesize that the PG free formulation of DYNAPAR AQ 1ml may decrease the incidences of thrombophlebitis at the site of injection. Moreover, faster delivery of drug to the circulation via bolus route will lead to immediate pain relief in comparison with conventional large volume (75mg/3ml) formulation of diclofenac that need to be diluted and buffered before administration.

To test our hypothesis, the present study was designed to evaluate the efficacy and safety of IV bolus injection of diclofenac 75mg/1ml versus IV infusion of diclofenac 75mg/3ml in the management of postoperative pain.

MATERIAL AND METHODS: This randomized, multicentre, assessor blind, single dose phase-III clinical study was conducted in India and data were collected from Department of Anesthesiology, CSM Medical university, Lucknow; Department of Anesthesia, D.Y. Patil Medical College, Hospital and Research Centre, Mumbai; R G Stone Urology and Laparoscopy Hospital, New Delhi; Dept. of Anesthesiology, Seth G S M C & K E M H, Mumbai ; Dept. of General Surgery, Dr. D.Y. Patil Hospital and Research Centre, Pune; Command Hospital, Central Command, Lucknow; Department of Anesthesia, Pain management and per-operative care, Fortis Hospital New Delhi.

This study was initiated at each centre after obtaining written approval from respective ethics committee and study was registered on clinical trial registry-India (CTRI) before first patient enrolment (CTRI registration number: CTRI/2010/091/ 000096). This study was conducted according to the protocol approved by office of Drug Controller General of India and Ethics Committees.

The study was also conducted in compliance with the ethical standards laid down in the Declaration of Helsinki, 1964 and its later amendments; Good Clinical Practice (GCP) 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 (2006), New Delhi.

Patients of either sex aged 18-60 years, undergoing elective day surgery and requiring hospitalization for at least 12 hours post-operatively were screened for eligibility criteria during Aril 2010 to May, 2011. Patients suffering from moderate to severe post-operative pain (Visual analogue scale ≥ 4) were considered eligible for enrollment. All patients were explained the procedure clearly and written informed consent from each participant was obtained before their participation in the study. At the time of screening visit on the day before surgery, medical history was obtained; physical examination and laboratory investigations were performed. Medications considered necessary for the patients welfare and which does not interfere with the study medication were allowed.

Patients with mild baseline post-operative pain (Visual analogue scale <4) or known hyper-sensitivity to PG, diclofenac sodium any other NSAIDs or any component of either of the study formulations were excluded. Patients with history of bronchial asthma, peptic ulceration, bronchitis, coagulation disorder, mentally retarded and patients with compromised renal function were also excluded from the study at the time of screening. The women of child bearing age underwent the urine pregnancy test; the pregnant and lactating women were excluded in the present study.

Total 350 patients undergoing elective day surgery were recruited in the study as per eligibility criteria after obtaining written informed consent from each patient. The enrolled patients were identified only by randomization number, not by name or initials during the conduct of study in order to maintain confidentiality.

Enrolled subjects were divided into two groups as per computer generated simple randomization sheet. One group received diclofenac 75mg/1ml (Dynapar AQ, manufactured by Troikaa Pharmaceuticals Ltd, Ahmedabad, India) administered as IV bolus over a period of 5-60 seconds and other group received diclofenac 75mg/3ml (Voveran, manufactured by Novartis, India) administered as an IV infusion continuously over a period of 30 minutes.

Before starting the IV infusion, injection diclofenac sodium 75 mg/ 3ml was diluted with 100-500ml of either sodium chloride solution (0.9%) or glucose solution (5%), buffered with sodium bicarbonate (0.5 ml of 8.4% or 1 ml of 4.2% or a corresponding volume of a different concentration) taken from a freshly opened container. Only clear infusion solution was used. Intravenous infusion was administered through dedicated IV access immediately after dilution and buffering.

Both the study drugs were administered post-operatively when patient felt moderate to severe pain score (Visual analogue scale ≥ 4) after recovery from the anesthesia, the experienced pain was considered as baseline intensity of post-operative pain.

Primary efficacy endpoints were time to onset of analgesia and postoperative pain intensity while secondary efficacy endpoints included degree of pain relief and global assessment by patient and investigator. The safety endpoints were pain intensity and grade of thrombophlebitis at injection site. Safety and efficacy endpoints were evaluated over 12 hour study period.

The intensity of pain was assessed using Visual analogue scale (VAS) which had a rating from 0-10 with “0” indicating no pain and “10” worst possible pain. Safety and efficacy of both the study drug were evaluated over study period of 12 hours. Following administration of both the study drug, the time to onset of analgesia was assessed from each patient. Intensity of post-operative pain was assessed by using VAS at baseline (predose), 15 minutes, 30 minutes, 45 minutes, 1, 2, 4, 8 and 12 hours.

Degree of pain relief was assessed at 15 min, 1 hour and 12 hours after study drug administration using a 5- point verbal rating scale (0- No Pain Relief, 1- Mild Pain Relief, 2- Moderate Pain Relief, 3- Good Pain Relief, and 4- No Pain). Pain intensity at the site of injection was assessed using VAS at 1 hour, 8 hours and 12 hours after drug administration. Incidences of thrombophlebitis at the site of injection was assessed using 6 point grading scale at 1 hour 4 hours, 8 hours, 12 hours after drug administration.

Thrombophlebitis grading scale had rating from 0 to 5 where;

- 0 indicates "No Reaction";
- 1 indicates "Tenderness along vein";
- 2 indicate "Continuous tenderness or pain with redness";
- 3 indicate "Palpable swelling or thrombosis within length of cannula";
- 4 indicate "Palpable swelling or thrombosis beyond length of cannula";
- 5 indicate "as grade 4, but with overt infection".

Each patient was observed for any systemic adverse events during study period and the same was also recorded. At the end of study period, global assessment of treatment based on efficacy and tolerability was assessed by investigator and patients.

Sample size calculation was performed using software, PS Power and Sample Size Calculations Program, version no.3. Based on the study of diclofenac intradeltoid injection in patients with post-operative pain [9] a standard deviation (SD) of 2.74 was taken for intensity of post-operative pain as determined by visual analogue scale (VAS) score. To detect clinically significant difference of 1cm VAS score between two groups, the sample size was calculated at 90% power and at 5% level of significance using two sided test.

The desired number of patients in each group was 159. Considering a dropout rate of 10 %, 175 patients were required in each treatment group. Depending on the distribution of data appropriate parametric or non-parametric test was applied. Categorical data were presented as absolute number while quantitative data were presented as mean ± SD Unpaired "t" test was used to analyze the quantitative data of both the treatments groups. Chi-square test was used to compare the categorical or qualitative data of both the treatment groups.

All statistical analyses were performed using software, GraphPad prism, version no.5. *P* value of less than 0.05 was considered as significant.

RESULTS: Total 385 post-operative patients were screened at seven study centres. Among them 35 patient did not fulfill the eligibility criteria, hence 350 postoperative patients were enrolled and successfully completed the study. No patients were dropped out or discontinued due to any reasons. The data obtained from all 350 patients were subjected to stastical analysis. Demography and baseline characteristics (age, gender, weight, duration of surgery and baseline intensity of postoperative pain) were comparable among both the treatment groups **(Table 1).**

TABLE 1: DEMOGRAPHY AND BASELINE CHARACTERISTICS

Characteristic	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)	*P* value
Age (Year)	40.00±12.88	39.96±13.39	0.97*
Gender (Male/Female)	114/61	111/64	0.737**
Weight (Kg)	62.13±10.96	62.74±11.93	0.62*
Duration of surgery (in minutes)	91.07±58.44	100.28±61.91	0.154*
Baseline Pain Intensity (VAS score)	6.12±1.51	6.28±1.80	0.36*

Values are expressed in Mean ± SD for age, weight and VAS score; absolute number for gender (male /female); N = number of patients in treatment group. *Data were analyzed by unpaired 't' test **Data were analyzed by Chi square test

The mean time to onset of analgesia was significantly less in patients who received IV bolus injection of diclofenac 75mg/1ml as compared to IV infusion of diclofenac 75mg/3ml (10.46 ± 5.28 versus 20.36 ± 8.68 respectively, P<0.001, Mann Whitney test). There was gradual reduction in intensity of post-operative pain over a period of 12 hours in both the treatment groups as observed from the reduction trend in the VAS scores from baseline. However, intensity of post-operative pain in IV bolus group was significantly less than IV infusion group till 1 hour after study drug administration **(Table 2).**

TABLE 2: INTENSITY OF POSTOPERATIVE PAIN AS MEASURED ON VISUAL ANALOGUE SCALE (VAS)

Time points	Intensity of postoperative pain (VAS score)		*P* value
	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)	
15 Minutes	4.18±1.87	5.24±2.18	<0.001
30 Minutes	3.01±2.07	4.05±2.26	<0.001
45 Minutes	2.49±1.87	3.50±2.33	<0.001
1 Hour	2.13±1.70	2.97±2.24	<0.001
2 Hour	2.24±1.73	2.45±1.94	0.31
4 Hour	2.27±1.73	2.47±1.85	0.35
8 Hour	2.54±1.85	3.00±1.98	0.058
12 Hour	2.68±2.15	2.89±2.25	0.460

Values are expressed in Mean ± SD; N = Number of subject in treatment group. Data were analyzed by Mann Whitney test.

In addition, degree of pain relief in diclofenac 75mg/1ml IV bolus group was significantly more than IV infusion of diclofenac75mg/3ml at 15 minute and 1 hour after study drug administration **(Table 3).**

TABLE 3: DEGREE OF PAIN RELIEF

Time Points	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)	*P* value
15 Minutes	1.85±0.99	1.16±1.11	<0.001
1 hour	2.89±1.07	2.57±1.11	<0.001
12 hour	3.17±1.20	2.64±1.03	0.145

Values are expressed in Mean ± SD; N = Number of subject in treatment group. Data were analyzed by Mann Whitney test.

The patients who were treated with IV bolus injection experienced significantly lesser pain at the site of injection than the patients treated with IV infusion after 1 hour and 8 hours of study drug administration **(Table 4).**

TABLE 4: INTENSITY OF PAIN AT SITE OF INJECTION AS MEASURED ON VISUAL ANALOGUE SCALE (VAS)

Time Points	Intensity of pain at site of injection (VAS score)		*P* value
	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)	
1 Hour	1.36±1.30	2.14±2.09	<0.001
8 Hour	1.36±1.59	2.06±2.06	<0.001
12 Hour	1.75±2.30	1.99±2.35	0.366

Values are expressed in Mean ± SD; N = Number of subject in treatment group. Data were analyzed by Mann Whitney test.

Incidence and Grade of thrombophlebitis at injection site were significantly less in diclofenac 75mg/1ml IV bolus group than diclofenac 75mg/3ml IV infusion group at 1, 4, 8 and 12 hours after study drug administration (**Table 5**).

In diclofenac bolus group, only 2 patients had developed grade 2 or above thrombophlebitis while in diclofenac infusion group, 47 patients developed grade 2 or above thrombophlebitis**.**

TABLE 5: INCIDENCE AND GRADE OF THROMBOPHLEBITIS AT THE SITE OF INJECTION

Time Points	Diclofenac 75mg/1ml IV bolus (N = 175)		Diclofenac 75mg/3ml IV infusion (N = 175)		*P* value	
	n	Grade	n	Grade	*n**	Grade**
1 Hour	17	0.11±0.31	49	0.34±0.49	<0.0001	<0.001
4 Hour	33	0.18±0.45	77	0.57±0.63	<0.0001	<0.001
8 Hour	35	0.16±0.44	85	0.93±1.41	<0.0001	<0.001
12 Hour	38	0.17±0.42	90	1.03±1.46	<0.0001	<0.001

Values are expressed in Mean ± SD; N = Number of subject in treatment group. n= Number of patients developed thrombophlebitis up to time points; Data were analyzed by *Fisher's exact two-tailed test, **Mann Whitney test.

Significantly more number of patients in diclofenac 75mg/3ml IV infusion group (n= 85) required rescue medication as compared to diclofenac 75mg/1ml IV bolus group (n= 58). [48.57 % versus 33.14 %, *P* = 0.0033, Chi square test].

No cases of any unexpected and serious adverse events were observed during study period and the patient's safety was not compromised during the conduct of study. In IV bolus group, 4 patients reported nausea, vomiting and headache whereas in IV infusion group, 8 patients reported nausea, vomiting headache and fatigue. All the adverse events reported by the patients of both the treatment group were mild in nature and resolved without any sequelae.

Global assessment of treatment by patients and investigator significantly favored the IV bolus route of administration of diclofenac 75mg/1ml as compared to IV infusion route of diclofenac 75mg/3ml **(Table 6).**

TABLE 6: GLOBAL ASSESSMENT BY PATIENT AND INVESTIGATOR

Global Assessment	Patient's global assessment		Investigator's global assessment	
	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)	Diclofenac 75mg/1ml IV bolus (N = 175)	Diclofenac 75mg/3ml IV infusion (N = 175)
Excellent	94	16	110	17
Good	58	94	46	94
Fair	21	53	17	56
Poor	2	12	3	8
***P* value**	<0.001		<0.001	

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

DISCUSSION: In our study, both the route of diclofenac injection was effective in the management of postoperative pain. However, the patients treated with IV bolus injection of diclofenac experienced significantly faster onset of analgesia as compared to IV infusion of diclofenac. Similarly, improvement in pain intensity was significantly better with IV bolus administration till 1 hr after administration. This may be attributable to faster delivery of drug to the systemic circulation via bolus route of administration which results in significantly rapid pain relief. The delay in the time to onset of analgesia observed in IV infusion group may be due to slow delivery of drug into systemic circulation. The rapid onset of analgesia associated with IV bolus route of diclofenac 75mg/1 ml has clinically significant importance in management of acute pain where immediate relief is required.

The grade of thrombophlebitis and pain at the site of injection was significantly less in patients in diclofenac 75 mg/ 1ml IV bolus group as compared to the patients in diclofenac 75 mg/3 ml IV infusion group. Greater incidence of thrombophlebitis observed in IV infusion group can be attributed due to presence of PG in diclofenac 75mg/3ml injection. It has been well documented that the diclofenac preparation which contains PG, a co-solvent used for many poorly water soluble drugs, probably plays a major role in the development of venous thrombosis [7].

Incidences of thrombophlebitis have also been reported with other injections containing PG. Manila and his colleagues observed venous thrombosis following the use of diazepam containing PG [10]. Schou *et al*., studied the incidence of local reactions in hand and wrist veins following IV administration of diazepam in various solvents, including PG and lipid emulsion. The results of this study suggested that pain and thrombophlebitis at the site of injection occurred most frequently with the PG preparation [11]. Higher incidence of thrombophlebitis at injection site could be the reason for higher intensity of pain at the site of injection with IV infusion of diclofenac 75mg/3ml compared to IV bolus injection of diclofenac75mg/1ml.

Considering overall safety and efficacy evaluation of both the route of study drug administration, the patients' and investigator' global assessment scores were significantly more favorable towards IV bolus injection of diclofenac 75mg/1ml than IV infusion of diclofenac 75mg/3ml. This may be because of rapid onset of analgesia and better tolerability at the site of injection with diclofenac 75mg/1ml IV bolus injection.

The adverse events reported during study period were mild in nature and resolved without any squealae. No cases of any unexpected and serious adverse events were observed and reported during study period.

CONCLUSION: This study clearly suggested that IV bolus administration of diclofenac 75mg/1ml (Dynapar AQ) is better alternative to IV infusion in the management of post-operative pain with rapid onset of analgesia and better tolerability at the site of injection.

Moreover, the convenience associated with bolus injection of a ready to use formulation of Dynapar AQ results in time and cost saving as it does not contain PG which requires dilution and buffering before administration.

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