ORIGINAL ARTICLE

Subcutaneous Injection of Diclofenac for the Treatment of Pain Following Minor Orthopedic Surgery (DIRECT study): A Randomized Trial

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■ **Abstract**

Objectives: Parenteral diclofenac is frequently used for analgesia following minor orthopedic interventions. Currently available diclofenac formulations are for intramuscular (IM) or intravenous injection. A new 1 mL volume formulation of diclofenac containing hydroxypropyl-β-cyclodextrin (HPβCD) allows both SC and IM administration. The objective of this open-label, randomized, parallel group, active-controlled study was to assess the safety and efficacy of 75 mg diclofenac HPβCD, administered SC or IM, compared with IM Voltaren® 75 mg in inpatients undergoing minor orthopedic surgeries with moderate-to-severe postoperative pain.

Methods: A total of 325 patients were randomized to treatment. Surgery-related pain was comparable between groups before treatment and rapidly declined in all patients following diclofenac injection. The primary endpoint was investigator-assessed local tolerability up to 18 hours postinjection (redness, swelling, and hardening at the injection site each scored on a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe).

Results: Local tolerability was found to be optimal for all the injected formulations, with mean overall scores (0 to 9) of 0.57, 0.31, and 0.26, for diclofenac HPβCD SC, diclofenac HPβCD IM, and Voltaren® IM, respectively. Consistently, the overall tolerability as judged by the patients and investigators was reported as good or excellent in more than 90% of cases in all groups.

Conclusions: Overall, the study results indicate that safety and efficacy were similar irrespective of the diclofenac formulation used; thus, the new SC diclofenac HPβCD has an acceptable tolerability profile and may be considered a valid alternative to IM-delivered diclofenac formulations. ■

Key Words: diclofenac, subcutaneous, anti-inflammatory agents, nonsteroidal, assessment pain, drug administration routes, pain, postoperative, randomized controlled trial

INTRODUCTION

Diclofenac, a highly effective and well-tolerated nonselective NSAID, is recommended for use in the treatment of acute and chronic pain and inflammation.[1,2] Parenteral diclofenac, usually administered intramuscularly, is frequently used to deliver analgesia following minor orthopedic interventions[3] and relieve the acute pain and inflammation associated with dental and other minor surgery.[4] Currently available diclofenac formulations

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are formulated for intramuscular (IM) or intravenous (IV) injection* and usually contain 75 mg diclofenac sodium in a 3 mL volume.

There are a number of downsides to the IM delivery route, including the development of Nicolau syndrome, a rare form of tissue damage at the site of injection.[5] There are several other limitations of the IM route of drug delivery, many of which can be overcome by the use of the subcutaneous (SC) route. Potential advantages of SC injection include higher availability of body sites suitable for injection, the procedure being easier, potentially safer, and the opportunity for self-administration.[6]

A new (1 mL) formulation of diclofenac containing hydroxypropyl-β-cyclodextrin (HPβCD) as a solubility enhancer has been developed.† The smaller volume of injection allows SC injection in addition to IM administration, in contrast to the marketed formulations Voltarol® and Dyloject®, which are only available for IM and IV administration. While it is theoretically possible to deliver a 2 mL volume via the SC route, this is regarded as the upper limit and a lower volume injection is preferable.[6]

The objective of this study was to assess the safety and efficacy of diclofenac HPβCD 75 mg, administered SC (or IM), compared with Voltaren® 75 mg for IM administration in the treatment of pain following minor orthopedic surgery.

METHODS

Study Design and Patient Population

This was an open-label, randomized, parallel group, active-controlled multicentre study conducted at 22 centers in Italy. The study was approved by the independent ethics committee of each of the sites involved in the study and conducted in accordance with the Declaration of Helsinki and current Guideline on Good Clinical Practice.

Inpatients of both genders aged 18 to 65 years undergoing one of the following minor orthopedic surgeries: arthroscopic meniscectomy; arthroscopic removal of bone fragments; or surgical correction of hallux valgus were included in the study after providing written informed consent. Additional inclusion criteria included moderate-to-severe postoperative pain (≥ 40 mm on a 0 to 100 mm visual analog scale [VAS] within 6 hours of the end of surgery). Females of childbearing potential were required to have a negative urine pregnancy test and to be using appropriate contraception throughout the study. Acute local/systemic infections at the time of surgery were reasons for exclusion as was any postsurgical complication.

Patients with gastrointestinal, coagulation, hepatic, renal, cerebrovascular, cardiac, arterial, or psychiatric disorders were excluded, as were patients with clinically significant or unstable concurrent diseases that could be negatively affected by NSAID administration. Patients with a history of alcohol or drug abuse within the previous 12 months were excluded, as were pregnant or breast-feeding females.

Patients receiving chronic treatment with agents with the potential to confound the interpretation of analgesic outcomes, such as other analgesics, long-acting aspirin, opioids, muscle relaxants, monoamine oxidase inhibitors, other antidepressants, and corticosteroids, were excluded. Previous use of tranquillizers and antihistamines was not permitted, unless their use had started at least 6 months earlier with the dose unchanged throughout the trial. Any other concomitant medication that may interact with diclofenac or affect safety was considered a reason for exclusion. Patients with a history of hypersensitivity to diclofenac or other NSAIDs or to one of the study medication components were excluded. Patients were not eligible if they were deemed by the investigator to be unreliable, had been previously enrolled in this study, or had used any investigational drug/device or participated in any clinical trial in the previous 3 months.

The prophylactic administration of low molecular weight heparin products was permitted as well as ice applications, but only in the postoperative setting before inclusion, with no time limitation prior to the baseline assessment. The administration of a local anesthetic (ropivacaine or equivalent) was allowed in patients undergoing surgical correction of hallux valgus.

Surgery and Medication

Patients who met all inclusion and exclusion criteria were enrolled and randomized to treatment if they developed acute moderate-to-severe postsurgical pain within 6 hours after minor orthopedic surgery. Patients were sequentially assigned to the next available randomization number and received one of the 3 treatment groups: SC diclofenac HPβCD 1 mL, IM diclofenac HPβCD

*These include Voltarol® (Novartis Ireland Limited, Clonskeagh, Ireland), available in 3 mL ampoules containing 75 mg diclofenac sodium, and Dyloject® (Therabel Pharma UK Ltd., Maidenhead, U.K.) solubilised with hydroxypropyl β-cyclodextrin (HPβCD) and given in 2 mL.

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1 mL, and IM Voltaren® 3 mL. The randomization list was prepared by means of validated SAS® software (SAS Institute Inc., Cary, NC, U.S.A.) and stored in an electronic format.

Treatments were administered as single (SC or IM) injections in the upper part of the gluteus. The same injection area was selected for both the SC and IM injections for a consistent local tolerability evaluation at the site of injection.

Patients underwent a follow-up visit on day 2 (approximately 18 to 24 hours after treatment), and if needed, a second injection of the same treatment received on day 1 was given. A final visit was also undertaken approximately 1 week following patient discharge. In case of insufficient pain relief after 2 doses, the patient was withdrawn and received an alternative therapy.

Endpoints

The primary endpoint of the study was the mean overall local tolerability at the injection site as assessed by the investigator at 10, 30, 60, and 90 minutes and at 3, 6, and 12 to 18 hours after the first injection. Any presence of redness, swelling, and hardening was scored by means of 4-point severity scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The mean overall score was calculated by summing up each local tolerability score for redness, swelling, and hardening at any time point. The overall score therefore ranged between 0 (no local reaction) and 9 (severe local reaction).

Other safety variables included pain at the injection site assessed by the patient (on a VAS) immediately after the injection, at 10, 30, 60, and 90 minutes and at 3, 6, and, 12 to 18 hours after the first injection; overall opinion on local tolerability, as assessed by both patient and investigator at the end of day 2 by means of a 5-point verbal scale (4 = excellent; 3 = good; 2 = fair; 1 = poor; and 0 = none); laboratory parameters (hematology, blood chemistry, urinalysis) measured preoperatively or at day 1 and day 3; and vital signs (blood pressure, heart rate) measured at day 1, day 2, and day 7.

The analgesic efficacy of the treatments was also assessed during the study. A diary was provided to the patient soon after surgery for postsurgical pain assessments. Pain was assessed on a 0 to 100 VAS before treatment, and at 15, 30, 60, and 90 minutes and 3 and 6 hours after the first injection on the day of surgery. The number and percentage of patients requiring a second injection on day 2 was assessed, and overall efficacy according to both patient and investigator at the end of day 2 by means of the 5-point verbal scale described above was also examined.

Sample Size

The sample size calculation was based on a difference between test and reference treatments of 0.4 points in terms of mean overall tolerability score, corresponding to a low-medium effect size according to Cohen.[7] A standard deviation (SD) of approximately 0.30 was assumed from an earlier study.[8]

The sample size calculation indicated that 100 evaluable subjects per group would be required to provide the study with 80% power to reject the hypothesis of no difference between treatment groups and with a 2-sided alpha level of 0.05. A requirement for a total of 390 subjects was estimated to allow 300 evaluable subjects (100 per treatment group).

Statistical Methods

Comparisons between SC/IM diclofenac HPβCD and IM Voltaren® for the mean overall tolerability score and for each mean tolerability score (ie, presence of persistent redness, presence of persistent swelling, presence of hardening) were made using the Wilcoxon–Mann–Whitney *U*-test. The Van Elteren test was used to account for differences between centers. The median treatment difference and the 95% confidence interval (CI) were estimated using Hodges–Lehmann estimates. The primary endpoint was analyzed in both the intent-to-treat (ITT) and the per-protocol (PP) population.

Additionally, a responder analysis, considering an overall score of local tolerability equal to 0 as success, was performed by means of a chi-squared test. The chi-squared test (or Fischer's exact test) was also used for the between-group comparisons of the proportion of patients with adverse events (AEs) and for the overall opinion on local tolerability.

Pairwise comparisons between groups for the mean pain at injection site were made using an analysis of covariance (ANCOVA) model, with baseline value and center as covariates.

Vital signs and laboratory parameters were summarized using descriptive statistics, and 95% CIs for the changes from baseline were calculated. These comparisons were also made with an ANCOVA model.

For all primary and secondary variables, missing data were accounted for using the last observation carried

forward (LOCF) technique. The safety population was defined as all randomized patients who received study medication. The ITT population was defined as all randomized patients who received at least 1 dose of study medication and had at least 1 postbaseline primary endpoint assessment, while the PP population was defined as the ITT population excluding those patients who had major protocol violations.

RESULTS

A total of 342 patients were screened, and 325 were randomized to treatment between September 2008 and September 2009. The safety and ITT populations consisted of 325 patients. Of these, a total of 26 patients were considered major violators (12 in the diclofenac HPβCD SC group, 5 in the diclofenac HPβCD IM group, and 9 in the Voltaren® group). The most frequent reasons for violation were presence of a nonacceptable concomitant disease or condition (11 patients), noncompliance to the inclusion/exclusion criteria, such as a different surgical intervention (8 patients), or absence of development of moderate-to-severe pain within 6 hours from surgery (4 patients). The disposition of patients through the study and the reasons for withdrawal are outlined in Figure 1.

There were no marked differences between groups in patient demographics, vital signs, baseline pain score, and type of surgery (Table 1).

Efficacy Endpoints

Presurgical pain was comparable between groups, with the mean ± SD pain score (VAS) for the overall population being 56.15 ± 12.67. Pain rapidly declined after administration of diclofenac in all groups (Figure 2), and no significant difference was observed among the 3 treatment groups over the 6-hour observation period in either the ITT or PP populations.

Consistently, the number of patients requiring a second injection for persistent pain was comparable between the treatment groups, being 12 (11.0%), 18 (16.8%), and 14 (12.8%) in the SC diclofenac group, IM diclofenac group, and in the Voltaren® group, respectively.

The overall treatment efficacy was evaluated as good or excellent by most investigators and patients without any significant difference among groups (Figure 3).

Safety and Tolerability

The mean overall score of local tolerability (redness, swelling, and hardening) that could range from 0 (no

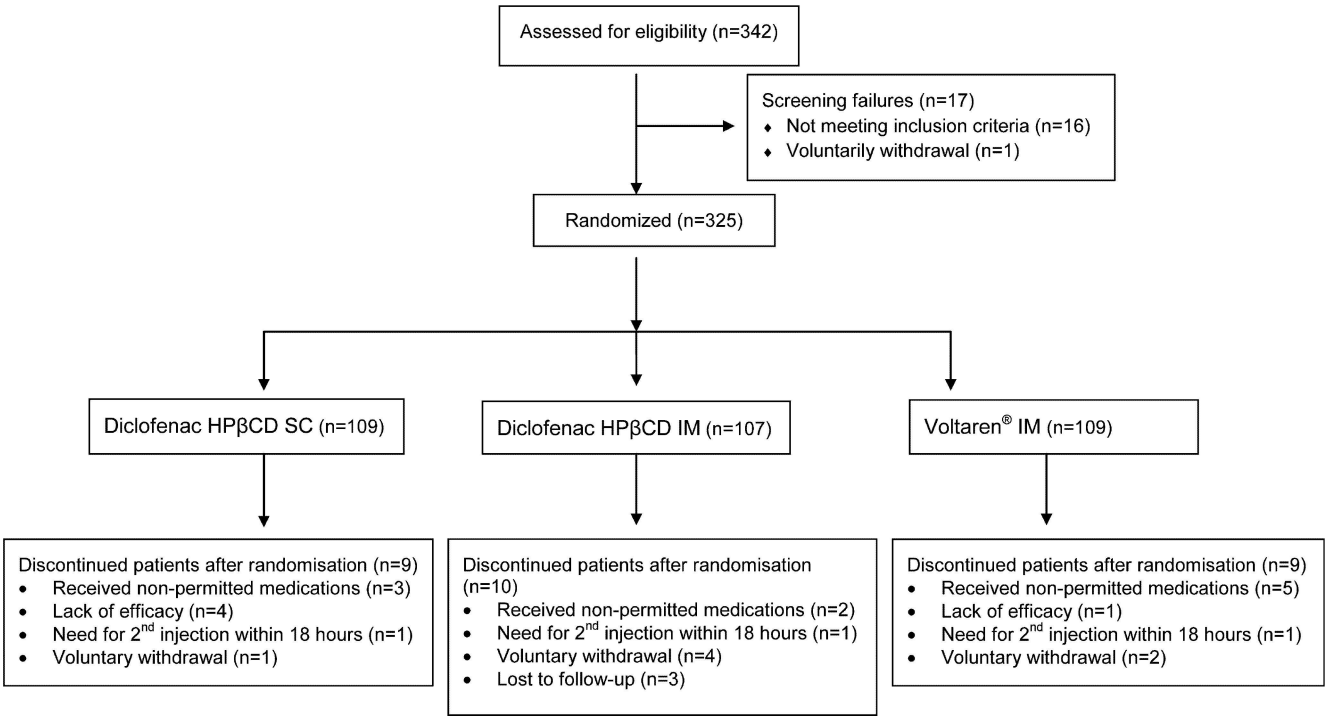

Figure 1. Participant flow. HPβCD, hydroxypropyl-β-cyclodextrin; IM, intramuscular; SC, subcutaneous.

Table 1. Demographics and Baseline Characteristics for the ITT Population

	Diclofenac HPβCD SC (n = 109)	Diclofenac HPβCD IM (n = 107)	Voltaren® IM (n = 109)	All Subjects (n = 325)
Sex (M/F)	33/76	31/76	34/75	98/227
Age				
Mean ± SD	43.81 ± 10.83	45.15 ± 10.97	43.73 ± 11.36	44.22 ± 11.04
Range	18 to 64	18 to 65	18 to 64	18 to 65
Race				
Caucasian	105	103	103	311
Asiatic	0	0	1	1
Black	4	2	2	8
Other	0	2	3	5
Systolic BP (mmHg) (Mean ± SD)	123.72 ± 12.16	121.24 ± 11.94	122.29 ± 12.26	–
Diastolic BP (mmHg) (Mean ± SD)	77.34 ± 8.89	76.94 ± 9.00	76.77 ± 8.29	–
Heart rate (bpm/min) (Mean ± SD)	71.37 ± 8.07	72.11 ± 7.74	72.36 ± 8.38	–
Predose pain intensity (VAS) (Mean ± SD)	56.51 ± 13.20	55.68 ± 12.04	56.25 ± 12.84	–
Type of surgery				
Arthroscopic meniscectomy	89	91	87	
Hallux valgus	16	14	17	
Arthroscopic bone fragment removal	0	0	3	
Other types of intervention	4	3	1	

SC, subcutaneous; IM, intramuscular.

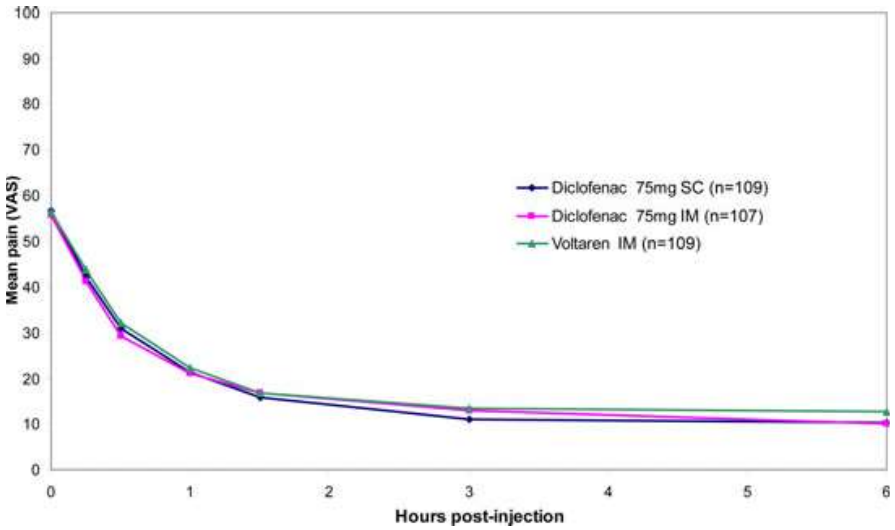

Figure 2. Postsurgical pain reduction. IM, intramuscular; SC, subcutaneous; VAS, visual analog scale.

reaction) to 9 (severe reaction) was 0.57 ± 1.09, 0.31 ± 0.66, and 0.26 ± 0.51 for SC diclofenac HPβCD, IM diclofenac HPβCD, and IM Voltaren®, respectively (ITT population). Similar values were observed in the PP population, being 0.60 ± 0.98, 0.32 ± 0.67, and 0.27 ± 0.52 for SC diclofenac HPβCD, IM diclofenac HPβCD, and IM Voltaren®, respectively.

The mean tolerability score decreased from 1.09 ± 1.86 at 10 min to 0.20 ± 0.79 at 12 to 18 hours with SC diclofenac HPβCD in the ITT population (Figure 4). Similarly, the mean score decreased from 0.78 ± 1.44 at 10 min to 0.05 ± 0.21 at 12 to 18 hours with IM diclofenac HPβCD and from 0.61 ± 1.17 at 10 min to 0.04 ± 0.23 at 12 to 18 hours with IM Voltaren®. The results observed in the PP analysis were comparable (data not shown). When the results of the overall tolerability score were analyzed, a statistically significant difference between SC diclofenac HPβCD and IM Voltaren® (P = 0.0459), and between SC diclofenac HPβCD and IM diclofenac HPβCD (P = 0.0283) was found in the ITT population, while no significant differences were found between groups in the PP population. Therefore, the results observed in the ITT population were not corroborated by the PP analysis.

When each local tolerability score (redness, swelling, and hardening) was analyzed separately, there was no

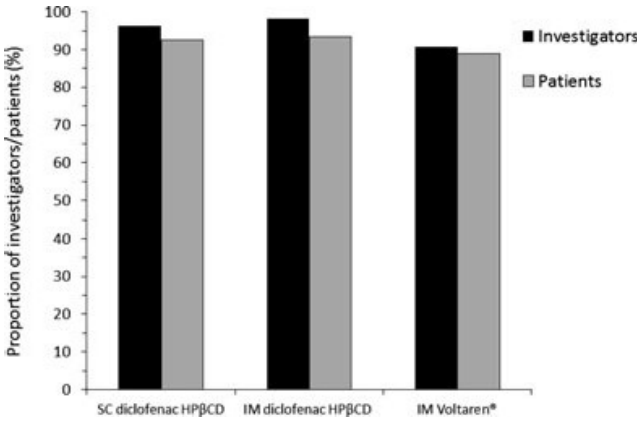

Figure 3. Proportion of investigators and patients rating treatment efficacy as good or excellent. HPβCD, hydroxypropyl-β-cyclodextrin; IM, intramuscular; SC, subcutaneous.

statistically significant difference between groups, except between SC diclofenac HPβCD and IM Voltaren® for persistent swelling in the ITT population (mean ± SD score: 0.19 ± 0.39 and 0.08 ± 0.20 in the SC diclofenac HPβCD and IM Voltaren® groups, respectively; $P = 0.017$).

The responder analysis in the ITT population revealed that 56% of patients in the SC diclofenac HPβCD group, 65.4% in the IM diclofenac HPβCD group, and 67.0% in the IM Voltaren® group did not report any local reaction after the injection, with no statistically significant difference between the treatments. Similar results were observed in the PP population (data not shown).

The results for "pain at the injection site" over time are presented in Table 2. Some statistically significant differences were found between SC diclofenac HPβCD and the IM injections ($P < 0.001$) immediately after the injection and at 10 minutes after the injection (SC diclofenac HPßCD vs. IM diclofenac HPßCD: $P = 0.004$; SC diclofenac HPßCD vs. IM Voltaren®: $P = 0.037$). However, pain at injection site decreased rapidly and nearly disappeared after the 10 minutes, and no further differences were found between all treatment groups.

The overall opinion on local tolerability was evaluated as good or excellent by more than 90% of the patients and investigators in all groups, both in the ITT and PP populations (Figure 5).

Overall, the proportion of patients with AEs and adverse drug reactions (ADRs) was numerically higher in the SC diclofenac group than in the IM Diclofenac and Voltaren® group, but the difference was not statistically significant (Table 3). Three serious AEs (SAEs) occurred

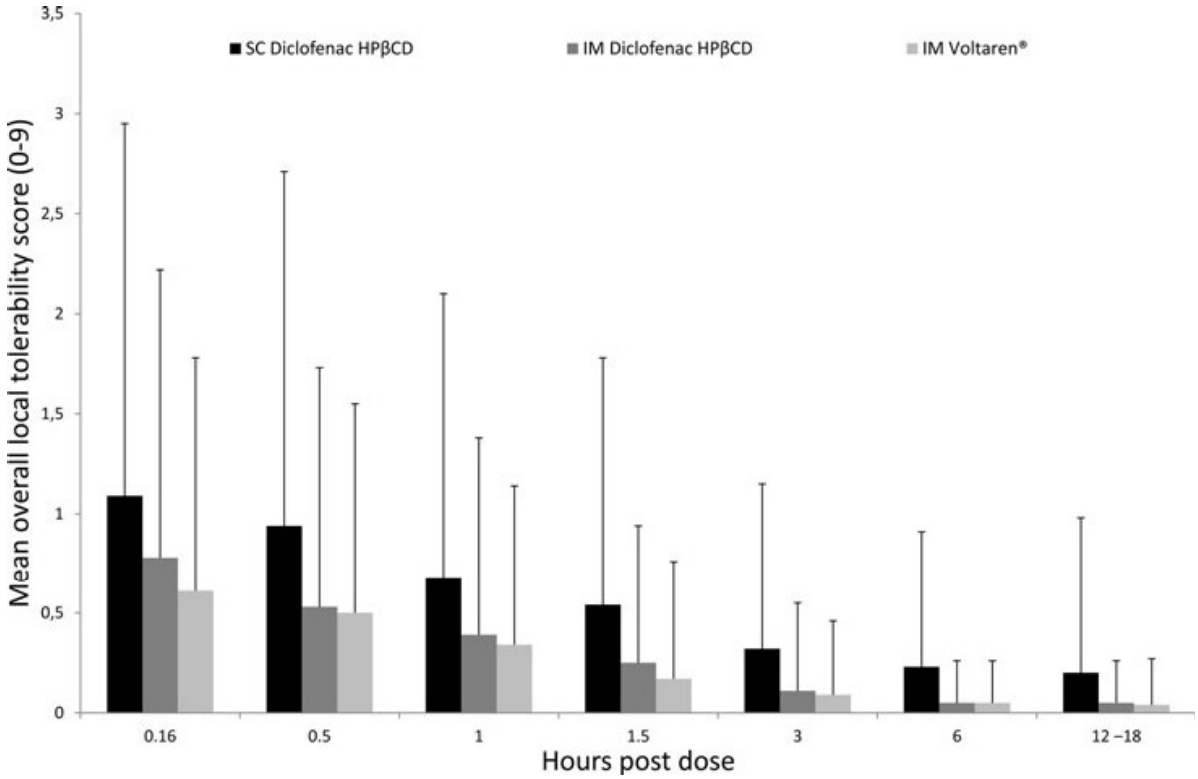

Figure 4. Overall mean tolerability score (0 to 9) up to 18 hours postdose (intent-to-treat population). HPβCD, hydroxypropyl-β-cyclodextrin; IM, intramuscular; SC, subcutaneous.

Table 2. Pain at the Injection Site Assessed by Patients Using the Visual Analog Scale (ITT Population)

	Diclofenac HPβCD SC (n = 109)	Diclofenac HPβCD IM (n = 107)	Voltaren® IM (n = 109)
Just after injection (Mean ± SD)	34.17 ± 26.71**,††	22.24 ± 21.65	18.24 ± 20.88
Time postinjection:(Mean ± SD)			
10 minutes	19.96 ± 21.40**,†	12.19 ± 17.20	10.29 ± 16.54
30 minutes	10.14 ± 16.56	7.88 ± 13.62	7.06 ± 13.54
1.0 hour	6.28 ± 12.49	6.17 ± 11.45	4.59 ± 9.43
1.5 hours	4.51 ± 10.01	4.80 ± 9.53	3.28 ± 6.80
3.0 hours	4.16 ± 8.75	3.46 ± 8.41	2.57 ± 5.01
6.0 hours	3.48 ± 8.20	2.89 ± 6.92	2.40 ± 4.83
12 to 18 hours	4.30 ± 9.19*	2.91 ± 7.50	2.03 ± 4.76

*P < 0.05, **P < 0.0001 vs. IM Voltaren®; †P < 0.05, ††P < 0.0001 vs. IM Diclofenac HPβCD.
SC, subcutaneous; IM, intramuscular.

in the study, which were considered not related to the study treatment. One was a postoperative myocardial thrombosis occurring in a patient randomized to SC diclofenac HPβCD. The SAE resolved following treatment. The other SAEs were a moderate chest pain and a mild fever occurring in 1 patient randomized to Voltaren® which again resolved after treatment. Overall, no patient discontinued due to the development of AEs.

Clinically significant changes in some liver enzymes were recorded in 9 patients, either pre-or posttreatment; these were considered treatment-related in 4 patients (2 patients each receiving SC diclofenac HPβCD and IM Voltaren®). No clinically significant changes in vital signs were recorded.

Of the patients experiencing ADRs (Table 3), almost all (90% to 95%) were administration site reactions, which were reported in 36 (33.0%), 25 (23.4%), and 26 (23.9%), subjects receiving SC diclofenac HPβCD, IM diclofenac HPβCD, and IM Voltaren®, respectively. Injection site pain occurred in 2 (1.8%), 4 (3.7%), and 1 (0.9%) patients in the SC diclofenac HPβCD, IM diclofenac HPβCD, and IM Voltaren® groups, respectively; all other ADRs occurred at a frequency of < 1%.

It should be noted that in this study, the procedures for AE reporting required that any tolerability score > 0 for redness, swelling, and hardening should be reported by the investigator as a treatment-related AE, independently from the real clinical relevance of the event itself.

DISCUSSION

The results of this safety and efficacy study demonstrate a similar local tolerability profile of the SC 75 mg diclofenac HPβCD formulation over the IM formulations.

The observed 0.3 difference in mean overall score for local tolerability between the SC and IM administration routes should be regarded as not clinically relevant considering that the mean tolerability score ranges from 0 (no reaction) to 9 (severe reaction). Moreover, the mean score was never significantly greater than 1 (mild reaction) with all treatments over the 12 to 18 hours postinjection. These mild local reactions disappeared within minutes/hours and recovered without the need for any countermeasure. The very good local tolerability profile is also confirmed by the responder analysis where more than 60% of the patients in any treatment group scored the local reactions as 0 (no reaction) attesting to

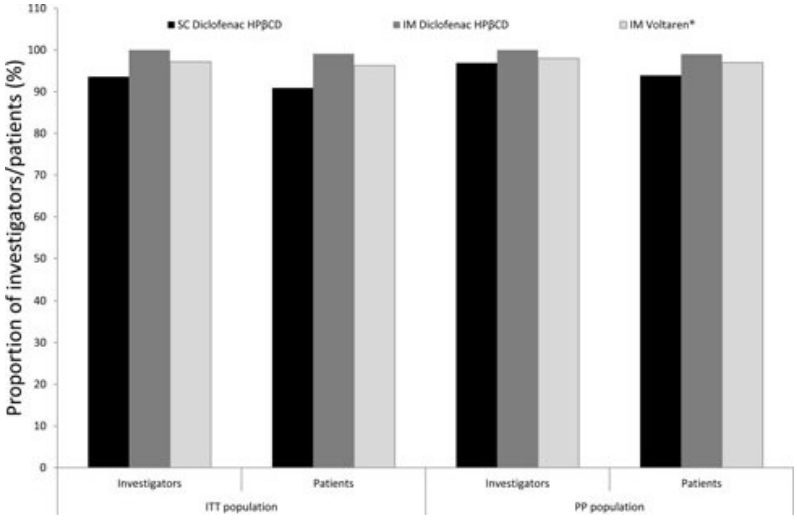

Figure 5. Proportion of investigators and patients rating local tolerability as good or excellent. HPβCD, hydroxypropyl-β-cyclodextrin; IM, intramuscular; SC, subcutaneous.

Table 3. Summary of AEs, ADRs, SAEs, and Clinically Significant Out-of-Range Values Observed in the Safety Population

	Diclofenac HPβCD SC (n = 109)	Diclofenac HPβCD IM (n = 107)	Voltaren® IM (n = 109)
No. AEs*	159	100	95
No. patients with AEs	47 (43.1%)	37 (34.6%)	40 (36.7%)
No. AEs leading to withdrawal	0	0	0
No. ADRs	109	65	64
No. patients with ADRs	38 (34.9%)	27 (25.2%)	29 (26.6%)
No. SAEs	1	0	2
No. patients with SAEs	1 (0.9%)	0 (0.0%)	1 (0.9%)
No. patients with clinically significant out-of-range laboratories	4 (3.7%)	1 (0.9%)	4 (3.7%)

*Defined as AEs considered either possibly, probably, or definitely related to treatments.
AE, adverse events; ADRs, adverse drug reactions; SAEs, serious adverse events; SC, subcutaneous; IM, intramuscular.

the good tolerability of both the SC diclofenac HPβCD formulation and IM formulations. Consistently, the patients' and investigators' evaluations on overall tolerability were recorded as good or excellent in more than 90% of cases in all treatment groups.

Localized reactions at the site of injection appeared to be somewhat more marked in patients treated subcutaneously as compared to those receiving the drugs intramuscularly. This finding was already observed previously with drugs administered subcutaneously (either active or placebo formulations)[9] and might well be due to the fact that SC injections are shallower, and therefore, local reactions such as swelling, hardening, and redness are more easily seen and felt than those occurring following deeper injections, as after IM administration. Muscle edema or hardening can be more difficult to palpate, and hematomas less visible.

Moreover, it should be noted that any tolerability score > 0 for redness, swelling, and hardening was required to be reported by the investigator as a treatment-related AE, independently from the real clinical relevance of the event itself. Therefore, the high reporting rate of AEs was an expected finding, and the incidence of administration site reactions reported in this study may be overestimated.

Pain at the injection site was generally mild immediately after injection and substantially reduced and almost absent 10 minutes from the injection, irrespective of the treatment and route. The significant difference observed during the first minutes after the injection between the SC diclofenac HPβCD, and the IM treatments is likely due to differences between SC tissue and muscle tissues in terms of both presence and distribution of nociceptors and pain threshold.[10–12]

With regard to the efficacy results, this study demonstrated a superimposable efficacy profile of the SC diclofenac HPβCD, the IM diclofenac HPβCD, and IM Voltaren®. Postsurgical pain rapidly declined after any treatment injection with no statistically significant differences observed between SC and IM diclofenac HPβCD and IM Voltaren® at any assessment time point.

Overall, there were no significant or clinically relevant safety concerns with this SC formulation. The availability of a parenteral diclofenac formulation that can be delivered subcutaneously is an advantage for some patients for a number of reasons. IM administration may not be appropriate in patients with inadequate muscle mass, for example.[6] SC injection is less likely than IM injection to pierce a blood vessel or cause nerve damage, as the larger blood vessels and major nerve fibers are located below the depth of penetration of the shorter needles used for SC injections.[6] Importantly, rare adverse complications in the form of tissue damage at the injection site (Nicolau syndrome) have been reported following IM administration of diclofenac sodium.[5,13]

This study supports the conclusion that diclofenac HPβCD and Voltaren® were both well tolerated and were not associated with any severe, persistent adverse reactions.

While this study was limited to patients with moderate-to-severe acute pain following minor orthopedic surgery, the new SC diclofenac HPβCD has also been studied in another validated acute pain model (pain following third molar extraction). In this dental surgery study, 3 dosages of SC diclofenac HPβCD were tested: 25 mg/mL; 50 mg/mL; and 75 mg/mL, with comparable profiles both in terms of analgesic efficacy and local tolerability. All the dosages showed excellent efficacy and tolerability profiles.[14] Therefore, taken together, the results of the present study and the previous study in dental pain support a role for SC diclofenac HPβCD in the treatment of acute pain.

CONCLUSION

The results of this study demonstrate that a single SC or IM injection of the 75 mg diclofenac HPβCD formulation has a similar efficacy and safety profile to the reference IM formulation, Voltaren®. SC administration of diclofenac HPβCD may therefore be a valid alternative to the classical IM route, with some potential practical advantages for the patient and the prescriber.

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