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Clinical and Laboratory Hematologic Findings in Patients Receiving Repeated-Dose Injectable HPβCD-Diclofenac for Acute Postoperative Pain: Pooled Analysis of Two Randomized Controlled Phase III Clinical Trials

Tong J Gan[1], Neil Singla[2], Stephen E Daniels[3], Douglas A Hamilton[4,5], Peter G Lacouture[6,7], Olufunmibi Johnson[8], Christian RD Reyes[8] and Daniel B Carr[4,9*]

[1]*Department of Anesthesiology, Stony Brook University, Stony Brook, NY 11794, USA*

[2]*Lotus Clinical Research, LLC, Pasadena, CA 91105, USA*

[3]*Premier Research, Austin, TX 78705, USA*

[4]*Javelin Pharmaceuticals, Inc., Cambridge, MA 02140, USA*

[5]*New Biology Ventures, LLC, San Francisco, CA 94133, USA*

[6]*Magidom Discovery, LLC, Lindenhurst, IL, 60046, USA*

[7]*Brown University School of Medicine, Providence, RI, 02912, USA*

[8]*Hospira, Inc, Lake Forest, IL 60045, USA*

[9]*Department of Anesthesiology, Tufts Medical Center, Boston, MA 02111, USA*

[*]**Corresponding author:** Daniel B Carr, Department of Anesthesiology, Tufts Medical Center, #298, 800 Washington Street, Boston, MA 02111, USA, Tel: 617-636-9710; Fax: 617-636-9709; E-mail: daniel.carr@tufts.edu

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Abstract

Objective: While the non-steroidal anti-inflammatory drugs (NSAIDs) represent an important option for the management of acute postoperative pain, their use can be limited due to potential safety concerns, including bleeding risks. This study examined the bleeding-related safety of injectable diclofenac formulated with hydroxypropyl-β-cyclodextrin (HPβCD-diclofenac) when used for postoperative pain management.

Methods: Data from two randomized, double-blind, placebo- and active comparator-controlled phase III trials were pooled. Patients in both studies received HPβCD-diclofenac, placebo, or the active comparator ketorolac via intravenous injection every 6 hours for ≤ 5 days following abdominal/pelvic or orthopedic surgery. Bleeding adverse events (AEs) were evaluated through the treatment period and follow-up (≤ 37 days), and relative bleeding AE risks (RR) were estimated. Changes in hematology laboratory values were also assessed.

Results: Overall, 608 surgical patients received ≥ 1 dose of study medication. Bleeding AEs occurred in n=9/318 (2.8%) patients receiving HPβCD-diclofenac, n=8/142 (5.6%) patients receiving ketorolac, and n=4/148 (2.7%) patients receiving placebo. Over the period examined, HPβCD-diclofenac was not associated with increased bleeding AE RR versus placebo (1.05 [0.33, 3.35]; p=0.93), nor was ketorolac (2.08 [0.64, 6.77]; p=0.22). Bleeding AEs were predominantly mild or moderate in severity. No treatment-related bleeding AEs occurred in the HPβCD-diclofenac group (1 in both the placebo and ketorolac groups). Among the subset of patients receiving concomitant anticoagulants, bleeding AEs occurred in n=3/60 (5.0%) patients receiving HPβCD-diclofenac, n=2/29 (6.9%) patients receiving ketorolac, and n=0/35 patients receiving placebo. In the HPβCD-diclofenac group, postsurgical shifts to low hematocrit and hemoglobin occurred in 35.7% and 28.3% of patients, respectively (versus 31.4% and 21.5%, respectively, with placebo). Postsurgical shifts in platelet count were uncommon (<3.0% across treatment groups).

Conclusions: While follow-up studies in larger populations are warranted, this analysis suggests that HPβCD-diclofenac may not present a significant incremental bleeding AE risk versus placebo when used for acute postoperative pain management.

Keywords: Postoperative pain; Non-steroidal anti-inflammatory drugs; Non-opioid analgesics; Safety; Orthopedic surgery; Bleeding; Multimodal analgesia

Introduction

Adequate treatment of acute pain following surgery is a key aspect of perioperative care, as under-treatment of acute pain can trigger greater use of healthcare resources and ultimately lead to poor outcomes, which can include the development of chronic postsurgical pain [1-5]. Intravenous (IV) non-steroidal anti-inflammatory drugs (NSAIDs) are considered an increasingly important element of postoperative pain management, either exclusively or as a component of a multimodal regimen [6-8]. Use of NSAIDs in combination with opioids in the postsurgical setting can contribute to reduced opioid consumption and lowered incidences of opioid-related adverse events (AEs) such as nausea and vomiting that can impede recovery, thereby helping to reduce hospital length of stay following surgery [9-15].

Though the efficacy of NSAIDs for the management of several painful conditions has been widely demonstrated, drugs in this class also carry potential concerns related to gastrointestinal (GI), hematologic, renal, and cardiovascular safety [16-20]. Owing to these concerns, NSAID-containing products include warnings outlining the GI, renal, and bleeding risks associated with NSAID use [21,22]. In addition, guidelines typically recommend limiting NSAID dosage and duration, as well as selection of NSAIDs based on individual patient risk assessments [8,20,23].

Specific bleeding risks related to NSAID use have largely been identified in the context of long-term or chronic use, which has been associated with increased risks of GI bleeding [23-27]. Factors such as advanced age, concomitant anticoagulant use, and longer-duration NSAID use have also been linked with increased bleeding-related AE risk in patients receiving NSAIDs [21,23-25,28-30]. Importantly, NSAID use has also been associated with potential bleeding-related complications when utilized postoperatively [31]. Thus, any new NSAID indicated for use in this setting must be carefully evaluated with respect to potential bleeding risks.

Diclofenac is an NSAID with equivalent inhibition of cyclooxygenase-1 (COX-1) and COX-2 and established efficacy, and is widely used to treat a number of painful conditions [32-34]. An injectable formulation of diclofenac solubilized with hydroxypropyl-β-cyclodextrin (HPβCD-diclofenac) does not require dilution and is administered as a low-volume bolus injection [35]. The efficacy and overall safety of HPβCD-diclofenac have been demonstrated in clinical trials examining single- and repeated-dose regimens for the treatment of acute postsurgical pain [36-42], and HPβCD-diclofenac is indicated for the treatment of mild-to-moderate pain when given alone, and moderate-to-severe pain when given alone or in combination with opioids.

Given the importance of understanding the potential bleeding risks associated with any NSAID, the objective of the current study was to conduct an in-depth examination of bleeding safety in patients receiving HPβCD-diclofenac for ≤5 days for the treatment of acute moderate-to-severe pain following abdominal/pelvic or orthopedic surgery. The study comprised an analysis of pooled AE and hematology laboratory data from two randomized, double-blind, placebo- and active comparator-controlled phase III trials in patients requiring IV analgesia for acute postsurgical pain [36,37].

Methods

For the trials included in this analysis (clinicaltrials.gov identifiers NCT00448110, NCT00507026), all patients provided IRB-approved written informed consent. Detailed methods for the individual studies are presented in Gan et al. [37] and Daniels et al. [36]. For both studies, sample size was based on calculated values defining the number of patients required to detect a clinically significant difference in the study's primary efficacy measure.

Patients

Per individual study protocols, patients were screened for inclusion if they were scheduled for abdominal/pelvic or orthopedic surgery requiring IV analgesia for the management of postoperative pain. Key patient inclusion criteria included age 18-65 years in the abdominal/pelvic surgery study and 18-85 years in the orthopedic surgery study, and the presence of moderate-to-severe patient-reported pain within 6 hours following surgery (pain intensity ≥ 50 mm on the 0-100 mm visual analog scale (VAS)). Females of childbearing age were required to have a negative pregnancy test at screening, as well as be practicing abstinence/using an approved contraception method. Patients were excluded from either study if they had a history of uncontrolled chronic disease contraindicating study participation, recent history (≤ 6 months) of cardiovascular events such as myocardial infarction (MI) or stroke, known allergy to diclofenac, NSAIDs, morphine, anesthetics, or any of the excipients of the study preparation, clinically significant lab or electrocardiography (ECG) result at baseline or screening, or had taken monoamine oxidase inhibitors, tryptophan, carbamazepine, or valproate ≤ 2 weeks prior to the study period. Aspirin (except for anti-platelet cardiac protection), NSAIDs, and other common analgesic drugs, centrally acting adjuvants, tranquilizers, or antihistamines were to be discontinued 24 h prior to study drug administration, and long acting NSAIDs or COX-2 inhibitors were to be discontinued 3 days prior to surgery.

Study design and outcomes

Both studies were multi-center, randomized, double-blind, placebo- and active comparator-controlled, repeated-dose, parallel-group phase III studies. In each study, patients were randomized to receive either HPβCD-diclofenac, ketorolac, or placebo, based on a computer-generated random number code. Clinical staff and patients were blinded to treatment group assignment (dose levels of individual study treatments in the orthopedic surgery population, however, were not blinded). All study medications were given as an IV bolus, with the first dose given ≤ 6 h following surgery and subsequent doses given every 6 hours until discharge or withdrawal/discontinuation (maximum 5 days post-first dose). Rescue medication (bolus IV morphine) was available upon patient request, up to once every 3 h after the initial study drug dose. If rescue medication did not provide adequate analgesia, the patient was withdrawn and given pain medication in accordance with the investigator's usual practice.

In the abdominal/pelvic surgery study, patients were randomly assigned to receive either 18.75 mg or 37.5 mg HPβCD-diclofenac, 30 mg ketorolac, or placebo (saline). In the orthopedic surgery study, patients randomly assigned to the HPβCD-diclofenac group received a dosage of either 37.5 mg (standard dose), 18.75 mg (high-risk patients, based on age ≥ 65 years, preexisting renal insufficiency, or presence of NSAID-related GI risk factors), or 50 mg (high-weight (≥ 95 kg), no risk factors). Similarly, dosage in the ketorolac group was based on the absence or presence of risk factors (no risk factors and high-weight patients: 30 mg; high-risk patients: 15 mg).

Safety assessments

Overall safety assessments included physical examination, clinical laboratory tests, vital signs, 12-lead ECG, and AEs. Treatment-emergent bleeding AEs were recorded from baseline through a 30-37 day follow-up period, and were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. Hematology laboratory measurements (hemoglobin, hematocrit, erythrocytes, leukocytes, lymphocytes, neutrophils, platelets) were obtained at screening, 24 h post-first study drug dose, and at discharge or early termination (and in addition, at 5-9 days following first study drug dose in the abdominal/pelvic surgery study). For a given hematology measure, a shift to high was defined as a shift from a value within or below the normal range at screening to a value above the normal range during the study period. A shift to low was defined as a shift from a

normal or high value at screening to a value below the normal range during the study period.

Statistical analysis

Safety analyses were performed on the pooled intent-to-treat (ITT) populations from both studies using SAS (Cary, NC, USA) version 9.1 or later. AE incidences were evaluated for all treatment groups, and relative risk (RR) ratios for active treatments versus placebo were calculated. RRs are presented as RR [95% confidence interval (CI)]. To further examine differences across treatment groups, p-values were calculated from ANOVA for numerical variables and Cochran–Mantel–Haenszel test for categorical variables. A p-value<0.05 was defined as statistically significant.

	HPβCD-diclofenac (n=318)	Ketorolac (n=142)	Placebo (n=148)	p-value[a]
Mean age, years (SD)	48.9 (14.1)	48.0 (14.7)	48.6 (14.1)	0.81
Gender				
Female, n (%)	233 (73.3)	107 (75.4)	107 (72.3)	0.83
Male, n (%)	85 (26.7)	35 (24.6)	41 (27.7)	
Procedure type[b]				
Abdominal/pelvic, n (%)	173 (54.4)	82 (57.7)	76 (51.4)	0.55
Orthopedic, n (%)	145 (45.6)	60 (42.3)	72 (48.6)	
Mean procedure duration, h (SD)	1.17 (0.69)[c]	1.13 (0.65)[d]	1.19 (0.71)	0.76
Mean doses received (SD)	7.3 (3.4)	7.5 (3.5)	6.2 (3.7)	--
1-6 doses, n (%)	101 (31.8)	43 (30.3)	71 (48.0)	--
7-8 doses, n (%)	150 (47.2)	67 (47.2)	53 (35.8)	--
>8 doses, n (%)	67 (21.1)	32 (22.5)	24 (16.2)	--
Concomitant anticoagulant				
No, n (%)	258 (81.1)	113 (79.6)	113 (76.4)	--
Yes, n (%)	60 (18.9)	29 (20.4)	35 (23.6)	0.49
Heparin, n (%)[e]	53 (16.7)	25 (17.6)	33 (22.3)	0.33
Coumadin, n (%)	12 (3.8)	6 (4.2)	4 (2.7)	0.77
Warfarin, n (%)	1 (0.3)	0	0	--
Concomitant medication with potential anticoagulant effects[f]				
No, n (%)	180 (56.6)	71 (50.0)	81 (54.7)	--
Yes, n (%)	138 (43.4)	71 (50.0)	67 (45.3)	0.42

[a]From ANOVA for numerical variables and Cochran–Mantel–Haenszel test for categorical variables;

[b]Most common procedures (>5% of subjects in all treatment groups): abdominal hysterectomy, abdominal surgery, bunionectomy/foot bone, inguinal hernia repair, knee replacement, vaginal hysterectomy, other;

[c]n=316;

[d]n=141;

[e]Includes heparin, heparin sodium, enoxaparin, enoxaparin sodium, Lovenox;

[f]Includes acetic acid derivatives and related substances, heparin, other antithrombotics, oxicams, platelet aggregation inhibitors, propionic acid derivatives, salicylic acid and derivatives, vitamin K antagonists (Coumadin, warfarin).

Table 1: Summary of baseline demographics and surgical characteristics. SD=standard deviation

Results

Study population

In total, n=608 patients undergoing an orthopedic or abdominal/pelvic procedure were included in the analysis (n=318, 142, and 148 patients in the HPβCD-diclofenac, ketorolac, and placebo groups, respectively). The three treatment groups did not differ significantly with respect to mean patient age, procedure duration, or proportion of patients who were female, underwent an abdominal/pelvic or orthopedic procedure, or received concomitant anticoagulants (heparin, Coumadin/warfarin; Table 1). Similarly, when the proportion of patients receiving any medication with potential anticoagulant effects was examined, there were no significant differences across treatment groups.

	HPβCD-diclofenac (n=318)	Ketorolac (n=142)	Placebo (n=148)
Total bleeding AEs	11	8	6
Patients with ≥ 1 treatment-emergent bleeding AE, n (%)	9 (2.8)[a]	8 (5.6)	4 (2.7)[b]
Risk ratio vs. placebo [95% CI]	1.05 [0.33, 3.35]; p=0.93[c]	2.08 [0.64, 6.77]; p=0.22[c]	--
Bleeding AEs by preferred term, n (%)[d]			
Rectal hemorrhage	2 (0.6)	2 (1.4)	0
Incision site hematoma	0	3 (2.1)	0
Vaginal hemorrhage	1 (0.3)	0	2 (1.4)
Epistaxis	2 (0.6)	0	0
Eye hemorrhage	0	1 (0.7)	0
Hemarthrosis	1 (0.3)	0	0
Hematemesis	0	0	1 (0.7)
Hematocrit decreased	0	0	1 (0.7)
Hematoma	1 (0.3)	0	0
Hematuria	1 (0.3)	0	0
Hemoptysis	0	0	1 (0.7)
Hemorrhagic anemia	1 (0.3)	0	0
Hemorrhagic ovarian cyst	0	0	1 (0.7)
Periorbital hematoma	0	1 (0.7)	0
Petechiae	0	1 (0.7)	0
Total postoperative anemia AEs	7	2	3
Patients with postoperative anemia AE, n (%)	7 (2.2)	2 (1.4)	3 (2.0)
Risk ratio vs. placebo [95% CI]	1.09 [0.28, 4.14]; p=0.83[c]	0.69 [0.12, 4.10]; p=0.76[c]	--

[a]Includes 1 patient with 2 epistaxis events and 1 patient with 2 vaginal hemorrhage events;

[b]Includes 1 patient with 1 event each of hematemesis, hematocrit decreased, and hemoptysis;

[c]From Cochran–Mantel–Haenszel test comparing treatment and placebo;

[d]n (%) represents number and percentage of patients with a given bleeding AE.

Table 2: Summary of treatment-emergent bleeding-related adverse events in the study population. AE = adverse event; CI = confidence interval.

Bleeding adverse events and hematology laboratory findings

Bleeding AEs were relatively uncommon across the study population (Table 2). In total, 11 bleeding AEs occurred in n=9/318 patients (2.8%) in the HPβCD-diclofenac group, 8 bleeding AEs occurred in n=8/142 patients (5.6%) in the ketorolac group, and 6 bleeding AEs occurred in n=4/148 patients (2.7%) in the placebo group. This included two patients in the HPβCD-diclofenac group who experienced 2 bleeding AEs (one patient with two epistaxis events, one patient with two vaginal hemorrhage events), and one patient in the placebo group who experienced 3 bleeding AEs (hematemesis, hematocrit decreased, and hemoptysis). In the HPβCD-diclofenac group, all bleeding AEs occurred in patients who underwent a surgical procedure <2 h in duration, n=7/11 AEs were in

orthopedic surgery patients, and n=9/11 were in patients ≤ 65 years old. Additionally, n=10/11 bleeding AEs in the HPβCD-diclofenac group occurred in patients receiving ≥ 7 doses (n=217 total patients). Similarly, n=5/8 bleeding AEs in the ketorolac group occurred in patients receiving ≥ 7 doses of ketorolac (n=99 total patients).

The overall bleeding AE risk was not significantly increased or decreased with HPβCD-diclofenac versus placebo (RR: 1.05 [0.33, 3.35]; p=0.93). Ketorolac was likewise not associated with a significant difference in bleeding AE risk versus placebo (RR: 2.08 [0.64, 6.77]; p=0.22). The most common bleeding AEs in the pooled population were rectal hemorrhage (n=2 patients receiving HPβCD-diclofenac and n=2 patients receiving ketorolac) and incision site hematoma (n=3 patients in the ketorolac group). In addition to bleeding AEs, the incidence of postoperative anemia was likewise low (n=7/318 patients (2.2%), n=2/142 patients (1.4%), and n=3/148 patients (2.0%) in the HPβCD-diclofenac, ketorolac, and placebo groups, respectively).

	HPβCD-diclofenac (n=318)	Ketorolac (n=142)	Placebo (n=148)
Bleeding AE severity			
Number of patients with AE that was:			
Mild, n (%)	6 (1.9)	7 (4.9)	2 (1.4)
Moderate, n (%)	2 (0.6)	1 (0.7)	2 (1.4)
Severe, n (%)	1 (0.3)[a]	0	0
Relationship to treatment			
Not related to treatment, n (%)	9 (2.8)	7 (4.9)	3 (2.0)
Treatment-related, n (%)	0	1 (0.7)[b]	1 (0.7)[c]

[a]Hematoma in a patient who underwent abdominal hysterectomy;

[b]Incision site hematoma in a patient who underwent partial colectomy;

[c]Hematemesis in a patient who underwent bunionectomy/foot bone procedure.

Table 3: Summary of bleeding adverse events by severity and relationship to treatment. AE = Adverse Event.

The majority of bleeding AEs were mild or moderate in severity, with only 1 AE judged to be severe (hematoma in a female patient who underwent abdominal hysterectomy and received HPβCD-diclofenac; Table 3). Similarly, only two bleeding AEs were judged to be treatment-related (incision site hematoma in a patient in the ketorolac group; hematemesis in a patient who received placebo) and both were mild in severity.

Among patients receiving concomitant anticoagulants, bleeding AEs occurred in n=3/60 patients (5.0%) receiving HPβCD-diclofenac, n=2/29 patients (6.9%) receiving ketorolac, and n=0/35 patients receiving placebo (Table 4; p=0.19 and p=0.11 for HPβCD-diclofenac and ketorolac versus placebo, respectively). On expansion of this analysis to include all concomitant medications with potential anticoagulant effects, bleeding AE incidences were 3.6% (n=5/138), 4.2% (n=3/71), and 1.5% (n=1/67) for the HPβCD-diclofenac, ketorolac, and placebo groups, respectively (p=0.39 and p=0.35 for HPβCD-diclofenac and ketorolac versus placebo, respectively).

With respect to timing relative to anticoagulant use, all bleeding AEs but one appeared to be concurrent with anticoagulant use, i.e., AE onset was on the same day as the anticoagulant was first received or prior to the last day of treatment with the anticoagulant (Supplemental Table 1). The lone exception was an incidence of incision site hematoma in a patient in the ketorolac treatment group, for whom the AE occurred on postsurgical day 8, one day following the end of the patient's enoxaparin sodium regimen for DVT prophylaxis; this AE was judged by the investigator to be treatment-related.

	HPβCD-diclofenac (n=60)	Ketorolac (n=29)	Placebo (n=35)
Patients receiving anticoagulants[a,b]			
Total bleeding AEs	4	2	0
Patients with ≥ 1 treatment-emergent bleeding AE, n (%)	3 (5.0)	2 (6.9)	0
Bleeding AEs by preferred term, n (%)			
Epistaxis	1 (1.7)[c]	0	0
Hematuria	1 (1.7)	0	0
Incision site hematoma	0	1 (3.4)[d]	0
Rectal hemorrhage	1 (1.7)	1 (3.4)	0

[a]Includes heparin and vitamin K antagonists (Coumadin/warfarin);

[b]For patients receiving any medication with potential anticoagulant effects (includes acetic acid derivatives and related substances, heparin, other antithrombotics, oxicams, platelet aggregation inhibitors, propionic acid derivatives, salicylic acid and derivatives, vitamin K antagonists), incidences of bleeding AEs were 3.6% (n=5/138), 4.2% (n=3/71), and 1.5% (n=1/67) for the HPβCD-diclofenac, ketorolac, and placebo groups, respectively;

[c]Includes 1 patient with two separate AEs of epistaxis;

[d]AE judged by investigator to be related to treatment

Table 4: Summary of bleeding adverse events in patients receiving anticoagulants. AE = adverse event.

Among the most common hematology laboratory parameter shifts occurring in the pooled study population were shifts to low hematocrit and hemoglobin levels. Among patients receiving HPβCD-diclofenac, a shift to a low hematocrit or hemoglobin level during the study period occurred in 35.7% and 28.3% of patients, respectively (versus 31.4% and 21.5%, respectively for placebo and 47.6% and 38.4%, respectively for ketorolac; Figure 1). Shifts in platelet counts were relatively uncommon (<3.0% in all treatment groups). Neutrophil and leukocyte counts were the most common laboratory parameters to demonstrate a shift to high values during the study period (Supplemental Figure 1). Stratification of patients revealed a general trend toward more frequent shifts to low hemoglobin , low erythrocytes, and low lymphocytes with increasing age for all treatment groups, and a trend toward more frequent shifts to low hemoglobin and low erythrocytes with longer surgery duration.

Discussion

Bleeding risks are a key concern both with NSAID use and in the context of surgery. As a surgical complication, bleeding can be associated with increased morbidity and mortality [43]. The results of this pooled analysis of data from two phase III placebo- and active

comparator-controlled clinical trials reveal a relatively low incidence of bleeding AEs among patients receiving HPβCD-diclofenac for ≤ 5 days for the management of acute postsurgical pain. During this acute treatment timeframe, there was no significant difference in bleeding AE risk with HPβCD-diclofenac versus placebo. The low incidence of treatment-emergent bleeding AEs (2.8%) and lack of treatment-related bleeding AEs in patients receiving HPβCD-diclofenac are in line with data from an open-label phase III safety study in which n=32/971 surgical patients (3.3%) receiving HPβCD-diclofenac had a bleeding-related AE and a total of 2 treatment-related bleeding AEs occurred [38]. Notably, the open-label safety study included large proportions of at-risk patients (35% of patients were ≥ 65 years old, and >60% received concomitant anticoagulants). Furthermore, the reported bleeding-related AE rates in the present study are consistent with rates reported for similar surgical groups in large retrospective studies [43,44].

In addition to factors such as age and preexisting medical conditions, postoperative or concomitant use of NSAIDs and anticoagulants has been identified as a risk factor for clinically relevant bleeding AEs [45,46]. In light of this important consideration, the present study examined bleeding AE incidences in patients receiving anticoagulants (heparin, coumadin/warfarin), as well as all drugs with potential anticoagulant effects. Though the overall number of patients receiving anticoagulants in each treatment group was relatively limited, none of the AEs occurring in patients receiving a concomitant anticoagulant was judged to be severe by the study investigator. All but one bleeding AE in this group appeared to occur concurrently with anticoagulant treatment, suggesting a potential contribution of anticoagulant treatment to the observed AEs. It is important to note, however, that an open-label large phase III HPβCD-diclofenac safety study found no difference in bleeding-related AE incidence between patients receiving and not receiving concomitant anticoagulants [38].

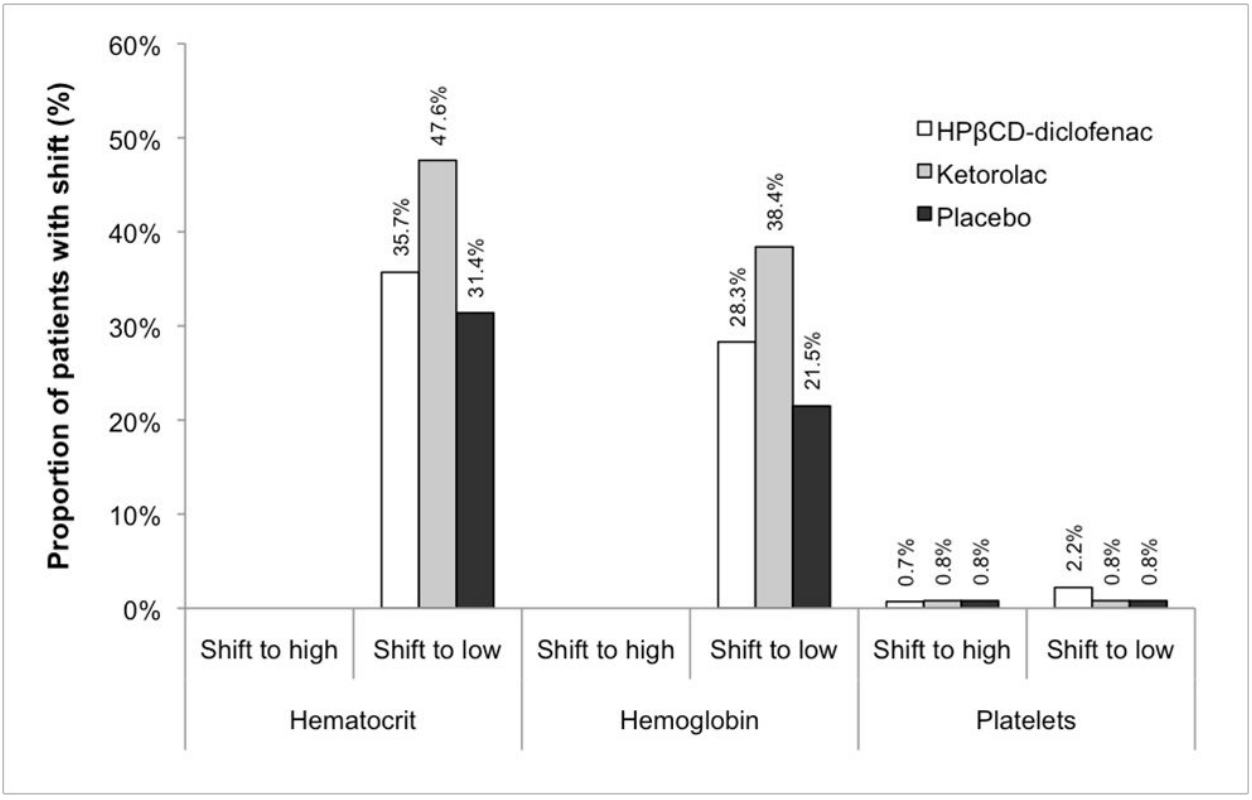

Figure 1: Summary of hematology laboratory shifts from baseline in the study population. The number of patients with a given shift tended to be lowest for patients receiving HPβCD-diclofenac and placebo. Shift to high = shift from normal or low value at screening to a high value during study. Shift to low = shift from normal or high value at screening to a low value during study. Hematocrit was measured in %, hemoglobin in g/L, and platelet count in 10^9/L. For each measurement, the total number of patients (HPβCD-diclofenac, ketorolac, placebo) was as follows: hematocrit (277, 124, 121); hemoglobin (279, 125, 121); platelets (274, 124, 120).

NSAIDs have also been reported to be associated with platelet function inhibition and increased perioperative bleeding [47]. However, data from healthy subjects have demonstrated that therapeutic dosages of diclofenac produce less GI damage and bleeding than aspirin, indomethacin, or naproxen, and have little effect on platelet aggregation or bleeding time [48]. Recently, a single-dose study demonstrated significantly less disruption of platelet function following administration of HPβCD-diclofenac than ketorolac or acetylsalicylic acid (ASA) [42]. This reduced effect of HPβCD-diclofenac on platelet function could be related to diclofenac's balanced inhibition of COX-1 and -2, as selective COX-1 inhibition is associated with GI and platelet adverse effects [42,49,50].

In addition to findings in line with previous studies of HPβCD-diclofenac, the bleeding AE rates observed in the present study compare favorably with those reported in previous studies of other IV NSAIDs and acetaminophen [18,21,46,51-58]. In one study of patients

undergoing major surgery, a 1.1% incidence of GI bleeding was reported in patients receiving ketorolac postsurgically (1.0% for the comparators diclofenac and ketoprofen) [46]. Similarly, a study in patients undergoing elective orthopedic and abdominal/pelvic surgical procedures found no increased risk of bleeding AEs in patients receiving IV ibuprofen versus placebo [57].

Further, the results of the present analysis support previous studies that suggest that diclofenac is not associated with added risk of postoperative bleeding complications versus placebo in the postsurgical setting [59-61]. Similarly, a study in patients undergoing transurethral prostate resection reported no added bleeding risk with the use of intramuscular diclofenac versus IV paracetamol [62]. It is important to note, however, that higher postoperative blood loss has been reported with administration of diclofenac versus placebo following breast surgery [63].

In addition to bleeding AEs, the prevalence of shifts in common laboratory hematology parameters was relatively low across treatment groups in the present study, and the shifts that were observed (e.g. an initial decrease in hemoglobin, increases in leukocyte and neutrophil counts) were in line with typical hematological shifts that can occur following surgical procedures [64-66].

In summary, the data from the present pooled analysis suggest that short-term postoperative use of HPβCD-diclofenac was not associated with significant bleeding risk versus placebo over the time window examined, with a similar overall finding for the active comparator ketorolac. The two studies included in the analysis were similar in terms of setting, drug dosage, dosing regimen, and safety analyses, which all lend themselves to an effective pooled analysis. Notably, the treatment regimen in the included studies was relatively brief (≤ 5 days, with most patients receiving ≤ 8 doses of study medication), and therefore does not represent long-term use, which is more typically associated with bleeding-related adverse events than acute postsurgical use [18,21,23,67-69]. The population size (608 total patients) represents a limitation of this analysis, such that conclusions about the relative safety of HPβCD-diclofenac with respect to bleeding must be inferred with caution. Still, the findings are supportive of the safety profile of repeated-dose HPβCD-diclofenac when used for short-term management of acute postoperative pain. This safety profile, in addition to the demonstrated efficacy of HPβCD-diclofenac for acute moderate-to-severe pain, suggest that this diclofenac formulation can play an important role in managing postsurgical pain in appropriate patient populations, particularly in light of the potential importance of acute pain management in avoiding unfavorable postoperative outcomes such as the transition to chronic postsurgical pain [70]. Future studies, including retrospective analyses of large postsurgical populations using electronic health (EHR) data may be able to provide further insight into the relative safety of HPβCD-diclofenac versus other IV analgesics with respect to bleeding and hematology outcomes.

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