Original Article

Oral Diclofenac Potassium Versus Hyoscine-N-Butyl Bromide In Reducing Pain Perception During Office Hysteroscopy: A Randomized Double-Blind Placebo-Controlled Trial

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Disclosure statement: The authors declare that they have no conflicts of interest and nothing to disclose.

Funding: None.

Clinical trial registry number: NCT02714699; ClinicalTrials.gov
Abstract:

Study Objective: To compare the efficacy of oral diclofenac potassium versus hyoscine-N-butyl bromide (HBB) in reducing pain perception in patients undergoing diagnostic office hysteroscopy (OH).

Design: Randomized double-blind placebo-controlled trial (Canadian Task Force I)

Setting: University Hospital.

Intervention: One-hundred twenty-nine patients were divided randomly into 3 groups (n=43 in each group); (group I) received 50 mg diclofenac potassium, group (II) received 20 mg HBB, and group (III) received placebo tablets. All tablets were taken orally 1 hour prior to OH. Primary outcome was the participant’s self-rated pain perception using the 10-point Visual Analogue Scale (VAS) during the procedure. Secondary outcomes included the VAS score 30 minutes after OH, ease of OH assessment using a 10 cm scale, duration of OH and adverse effects of the study medications.

Measurements and Main Results: Both of diclofenac and HBB groups showed significant pain scores reduction compared with placebo group (p=0.001). The mean pain score in diclofenac group was significantly lower than HBB group (2.12±1.03 vs. 3.02±1.55 respectively, p=0.002). Pain scores in diclofenac and HBB groups immediately after OH were significantly lower than placebo group (p=0.001) and the mean pain score in diclofenac group was significantly lower than HBB group (1.23±0.57 vs. 1.56±0.73 respectively, p=0.024). The ease of procedure score was significantly lower in diclofenac and HBB groups than the placebo group (p=0.003 &0.005, respectively). The mean duration of the procedure was significantly less in the diclofenac group (p=0.01). Fourteen women (32.6%) in the HBB group experienced dizziness and two women (4.6%) had nausea while only four women (9.3%) in the diclofenac group had dizziness and two women (4.6%) had vomiting.

Conclusion: Oral diclofenac potassium administration 1 hour prior to diagnostic OH reduces the procedure pain with subsequent easier and shorter OH duration. Oral HBB is less effective than diclofenac potassium with more adverse effects.
The trial is registered at Clinicaltrials.gov on March 21, 2016 with number NCT02714699 and available at:

https://clinicaltrials.gov/ct2/show/NCT02714699?term=NCT02714699&rank=1

Key words: Diclofenac potassium; Hyoscine-N-butyl bromide; Office hysteroscopy; Pain relief
Introduction:

Office Hysteroscopy (OH) is a gynecological minimally-invasive procedure that enables the physician to visualize the uterine cavity and identify endometrial abnormalities [1]. As an office procedure, it has many merits as lower cost, higher acceptability, lower complications rate and shorter recovery time [2]. Traditionally, diagnostic hysteroscopy depended on the use of vaginal retractors, cervical tenaculum, cervical dilators, and uterine distension media [3]. However, the outstanding improvements in instrumentation to minimize its calibre and implement the vaginoscopic approach made OH less painful and an easier procedure [4].

OH is well tolerated by many women; however, some experience excessive pain or discomfort leading to failure [5]. Pain could be related to passage of the hysteroscope through the cervical canal or distension of the uterus with fluid [6]. Cervical manipulation and uterine distension are associated with an excessive prostaglandin release.

Non-steroidal anti-inflammatory drugs (NSAIDs) are systemic analgesics inhibit the cyclooxygenase (COX) enzyme, thus reduce prostaglandins release. Although they are effective in decreasing pain in some gynecologic procedures [7], a recent meta-analysis [8] and a Cochrane systematic review [9] did not report any significant reduction of pain during OH with NSAIDs. On the contrary, The Royal College of Obstetricians and Gynecologists (RCOG) recommend administration of NSAIDs 1 hour before hysteroscopy to reduce the pain in the immediate postoperative period [10].

Hyoscine-N-butyl bromide (HBB) is an antispasmodic drug with peripheral anticholinergic effects on the biliary, gastrointestinal and genitourinary smooth muscles [11,12]. HBB could reduce the OH associated pain through relief of uterine spasms. Previous studies evaluating its analgesic effect during office gynecological procedures as saline infusion sonohysterography (SIS) and hysterosalpingo-contrast sonography (HyCoSy) failed to report significant pain relief [13,14]. However, we supposed that the use of low doses of HBB (10 mg) was insufficient to produce effective analgesia.
Additionally, the results of HBB in relieving labor pains, ureteric and intestinal colics encouraged us to evaluate its use in less painful procedure as OH.

As there is no clear consensus within the literature about the optimal method of pain relief during OH, the current study aims to compare the efficacy of oral diclofenac potassium versus oral HBB in reducing pain associated with diagnostic OH trying to find the most effective drug with the least adverse effects to be used before OH.

**Materials and Methods:**

**Study type, settings and duration**

The current study was a randomized, double-blind controlled trial registered at Clinicaltrials.gov on March 21, 2016 (NCT02714699) and available at: https://clinicaltrials.gov/ct2/show/NCT02714699?term=NCT02714699&rank=1. The trial was conducted at a tertiary University Hospital in the period between the 1st of October 2016 and the 31st of March 2017. The Institutional Ethical Review Board approved the study. Informed written consent was obtained from all women prior to enrollment in the study.

**Study participants**

We invited all women who attended the Outpatient Hysteroscopy Clinic during the study period to participate in the study. We included women with the following inclusion criteria: age between 18 and 50 years, body mass index (BMI) between 18 and 30 kg/m², American society of anesthesiologists (ASA) physical status I-II and had a clear indication for diagnostic OH as infertility, recurrent miscarriage or abnormal uterine bleeding.

We excluded women with suspected pregnancy, heavy vaginal bleeding, recent pelvic infection, postmenopausal women, those who received prostaglandins or analgesics prior to OH, and those known to have hypersensitivity or contraindication to NSAIDs. Lastly, women anticipated having difficulty in the procedure due to previous cervical surgery or stenosis were also excluded.

**Sample size**
Sample size was calculated based on a recent study reported mean pain score with OH in the placebo group was 5.92 [15]. We hypothesized that HBB will be at least as effective diclofenac in pain reduction. Sample size calculation was done prospectively using 1-Way ANOVA pairwise test using 80% power with α error of 0.05, a total sample size of at least 129 women in the three groups (43 in each group) would be necessary to detect 20% reduction in the pain score with the use of either diclofenac or HBB (OpenEpi, Version 3, open source calculator-SS Mean).

Allocation

Eligible participants were allocated to one of three groups. Group (I) women received 50 mg oral diclofenac potassium in the form of two tablets (Cataflam® 25 mg, Novartis Pharma. UK limited, Camberley, UK). Group (II) women received 20 mg oral HBB in the form of two tablets (Buscopan® 10 mg, Sanofi-Aventis Ireland Ltd. Dublin, Ireland). Group (III) women received two placebo tablets manufactured in the Department of Pharmaceuticals, Faculty of Pharmacy, Assiut University, Egypt. All tablets were taken under supervision of a study investigator orally 1 hour prior to OH. A single pharmacist was responsible for the manufacturing of the placebo tablets and packaging of all medications into sterile boxes with labeling them as A, B and C. Only the Pharmacist knew the type of medication in the boxes, so both the clinician and the women were blinded by the allocation group.

Randomization

Patients were randomized to three groups according to a three-blocked randomization list which was coded (A) or (B) or (C) at 1:1:1 ratio. The randomization list was prepared was done using a computer-generated random table. The allocated groups were concealed in serially numbered sealed opaque envelopes that were opened only after recruitment. Each envelope was labeled with a serial number and had a card noting the intervention type inside. A trained nurse had the envelopes and did not share in the patients’ counseling or care. The nurse opened the envelopes according to the order of attendance of women. Once allocation has been done, it could not be changed.
Study intervention

One of the study investigators collected the baseline data of all participants at the time of recruitment as age, BMI, parity, residence, educational level, history of dysmenorrhea or chronic pelvic pain, previous vaginal deliveries, cesarean sections and miscarriages. Then, he explained the standard 10-cm visual analog scale (VAS) to the participants for pain scoring [16]. The severity of pain was assessed with VAS (with 0= no pain and 10= worst imaginable pain). Finally, the patients’ blood pressure (BP) and pulse were measured before start and after the end of the procedure.

OH was carried out by the same clinician as an outpatient procedure using a rigid mini-hysteroscope has a diameter of 4 mm with continuous-flow diagnostic sheath and 2.9 mm, 30° angled telescope (Karl Storz®, Tuttlingen, Germany). The vagina was washed with povidone iodine solution and saline was used as a distension medium. After placing the woman in the lithotomy position, the hysteroscopy tip was positioned in the vaginal introitus, the labia being widened by fingers. The vaginoscopic approach was used to visualize the posterior fornix as well as the external cervical os in all women. When it was visible, the scope was moved forward carefully to the internal os and the uterine cavity without use of any speculum or tenaculum. After the gradual distension of the uterus, the tubal angles, fundus, anterior, posterior and lateral walls of the uterus were inspected in order and any abnormality was reported.

Intrauterine pressure of saline solution was kept to 50 mm Hg with an electronically controlled pump to prevent excessive distension of the uterine wall. Additionally, it was important to reduce the lateral movements at this stage in order to reduce patient pain and discomfort. The duration of OH was defined from introduction of the hysteroscope through the introitus till being out of it was recorded.

Study Participants were asked to report their pain scores at 4 times; before the procedure (anticipated pain), while the hysteroscope inside uterine cavity, immediately after the procedure at the time of getting the hysteroscope out of the introitus and 30 minutes after the end of the procedure using the same 10-point VAS. A trained nurse
gave the patient the VAS and asked her to mark the point she thought was corresponding to her pain on the graph at each time.

After the end of procedure, the clinician was asked to assess the ease of the procedure using a graduated VAS-like scale from zero to 10; in which 10 means terribly difficult procedure and zero means very easy procedure. All women were offered additional analgesics at 30 minutes after completing the procedure if needed. Patients were also asked to report any adverse effects.

**Study outcomes**

The primary outcome of the study was the difference in the mean VAS pain scores during OH between the study groups. The secondary outcomes included the mean VAS pain scores immediately and 30 minutes after OH, the clinician assessment of the ease of OH, the duration of OH and the adverse effects of the study medications.

**Statistical analysis**

Data were entered and statistically analyzed using SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA, version 22). Categorical data were presented as frequency and percentages. Chi-Square test was used for comparison between groups. Quantitative data were described as mean ± standard deviation. They were tested for normality by Shapiro-Wilkes test. In the normally distributed variables, one-way ANOVA test with LSD post-hoc multiple comparisons were used for comparison between groups. In the non-normally distributed variables, Kruskal-Wallis test was used for comparison between groups. P-value ≤0.05 was considered to be statistically significant.

**Results:**

One hundred forty-four women were approached to participate in the study. We excluded 13 cases; four had cardio-pulmonary diseases, three had an evidence of pelvic infection, three had an allergy to NSAIDs and three women had an intractable heavy vaginal bleeding. Additionally, two women refused to participate in the study (Figure 1; the study flowchart). All women were fully conscious and oriented throughout the procedure.
and no procedures were cancelled because of failure of hysteroscope introduction or uncooperative women.

All groups were comparable regarding the participants’ age, BMI, parity, residence, educational level, history of dysmenorrhea or chronic pelvic pain, number of previous vaginal deliveries, CS and miscarriages. The main indication of OH was either primary or secondary infertility in 69.7% of all study participants (Table 1). Figure 2 shows that there was no difference between the study groups regarding the patients’ pulse and BP before or after OH.

The mean VAS score for anticipated pain before the OH was almost 1 in the 3 groups with no statistically significant difference. The mean VAS score for maximum pain during OH was significantly lower in the diclofenac group than in placebo group (2.12 vs. 5.67; p=0.001). The mean difference between groups was 3.55, representing a 62% reduction in VAS score in the diclofenac group. Similarly, HBB group mean VAS score was significantly lower than placebo group (3.02 vs. 5.67; p=0.001). The mean difference between groups was 2.65, representing a 46% reduction in VAS score in the HBB group. Moreover, the mean VAS score in the diclofenac group was significantly lower than HBB group (2.12 vs. 3.02, p=0.002).

Immediately after OH, the mean VAS score remained lower in the diclofenac group compared with the placebo group (1.23 vs. 2.86; p=0.001) and the HBB group compared with the placebo group (1.56 vs. 2.86; p=0.001). However, the mean VAS scores were similar in all study groups at 30 minutes after OH (p=0.23). Both study groups showed a trend toward reduction in VAS score over time throughout the follow-up period. However, a much larger reduction in VAS score was present in the placebo group immediately and 30 minutes after OH, reflecting the higher initial VAS score during OH with the placebo (Figure 3).

The ease score of OH reported by the clinician differed significantly between the groups overall (p=0.001) (Table 2). It was highest in the placebo group, the difference was significant for the direct comparison with the diclofenac group (p=0.003) and HBB group.
Additionally, the duration of the procedure differed significantly between the groups overall (p=0.01). It was significantly longer in the placebo group in direct comparison with the diclofenac group (6.88 vs. 4.65 minutes; p=0.015) and HBB group (6.88 vs. 5.23 minutes; p=0.005), but there was no significant difference between diclofenac and HBB groups (p=0.08). No correlation was found between the duration of the procedure and pain scores (r=0.139, p=0.096). The proportion of women requested additional analgesia was significantly different among the groups overall (p=0.001), and in direct comparisons between groups (diclofenac vs. placebo; p=0.001, HBB vs. placebo; p=0.001, diclofenac vs. HBB; p=0.02).

Regarding the adverse effects of the study medications, fourteen women (32.6%) in the HBB group suffered from dizziness and two women (4.6%) had nausea. On the other hand, only four women (9.3%) in the diclofenac group had dizziness and two women (4.6%) had vomiting with no statistical significant difference regarding any adverse effects between all groups. No complications from the procedure were reported. Finally, no cases of failure of the procedure occurred in any group.

Discussion:

In the current study, oral administration of diclofenac potassium 50 mg one hour before outpatient OH significantly reduced the pain scores during and immediately after the procedure when compared with a placebo. Additionally, oral HBB 20 mg significantly reduced the pain scores but to a lesser extent than diclofenac potassium with more frequent adverse effects.

Pain during OH is multifactorial; application of the speculum, tenaculum on the cervical lip can induce severe pain. In addition, introduction of the rigid hysteroscope inside the uterine cavity can add to pain perception [7]. Pain transmitted from the uterus through two different visceral pain pathways; Parasympathetic (S2-S4) provides sensory innervation to the cervix and lower part of the uterus and sympathetic (T10-L1) provides sensory innervation to the uterine fundus [17]. Vaginoscopic approach is known to induce
less pain than traditional OH as the placement of speculum and application of tenaculum were skipped [18].

Many options for pain relief were reported in literature included oral and intravenous analgesia; either opioid or non-opioid (NSAIDs and paracetamol) analgesics. Local anesthetics applied through intrauterine, paracervical injection, topical spray, gel and cream were also evaluated [8]. However, previous studies for pain relief during OH reported no agreement on a specific effective analgesic either local or systemic [8]. In the current trial, we investigated the analgesic efficacy and safety of two modalities with different mechanisms of action; diclofenac potassium which is one of NSAIDs and HBB as an antispasmodic drug.

NSAIDs act mainly through decrease prostaglandins release therefore; they can be more effective in reducing pain after OH. A recent Cochrane systematic review published in 2017 included several trials studied the use of NSAIDs before OH [9]. Our results agreed with some of them that confirmed a valuable effect of NSAIDs use prior to OH. They recommended further trials to provide the necessary data on the efficacy of oral NSAIDs.

Tam and Yuen reported no difference between pain scores during and after OH in patients received oral diclofenac sodium 50 mg or placebo tablets 1-2 hours before the procedure [19]. Similarly, Hassa and his colleagues failed to find any difference in pain scores for women received rectal diclofenac sodium 60 min before OH and those received placebo (p=0.57) [20]. Moreover, they found no significant difference in patient (p=0.67), duration of OH (p=0.05) and post-procedural need for analgesia (p=0.71). Our results contradict both studies and this could be attributed to the difference in pharmacological properties of the used drug. Diclofenac potassium is generally considered to be more quickly absorbed and have a faster onset of analgesic activity than diclofenac sodium [21].

In another study, Pain scores during and immediately after OH in women received oral ketoprofen were significantly higher than misoprostol (p=0.02) [22]. Additionally,
Teran-Alonso and his colleagues reported no difference in pain scores between women who received paracetamol 1000 mg and ibuprofen 600 mg one hour before OH and those who did not receive any medication [23]. Even so, the RCOG recommended a standard dose of NSAIDs one hour before hysteroscopy to reduce the immediate postoperative pain [10]. This agrees with our results in which diclofenac potassium administration effectively reduced the pain after the procedure.

On the other hand, a recent study reported that celecoxib, which is one of the selective COX-2 inhibitors NSAIDs, led to significantly lower pain scores than placebo during OH (p=0.001), immediately after the procedure (p=0.016) and finally 30 min after OH (p=0.001) [15]. With exception of pain reduction at 30 min after OH, our results about diclofenac potassium are matched with their study results. The mean pain scores during and immediately after the procedure in our results with diclofenac potassium were even lower than those reported with celecoxib in their study (2.12±1.03 vs. 4.63±1.63 and 1.23±0.57 vs. 2.55±1.46, respectively).

HBB is an antispasmodic drug used for relief of muscle spasms. It acts mainly through blocking the transmission of neural impulses in the parasympathetic ganglia and inhibiting the cholinergic transmission in the synapses [24]. It is commonly used as analgesic in renal colic, intestinal colic and labor pains [25, 26]. Two studies previously evaluated its effect on pain perception during office gynecological procedures. The first reported no statistically significant difference in pain scores (median VAS; 5 vs. 4.5 in the HBB and placebo group, respectively, p=0.755) during SIS [13]. While the second reported no statistically significant difference in pain scores between the HBB and placebo groups during HyCoSy (p=0.807) [14]. This could be attributed to the lower dose of HBB (10 mg) used in both studies. In our study we used a dose of 20 mg HBB and we found that it has a positive effect in reduction of the pain during and immediately after OH.

One important confounding factor was that the long duration of OH may cause pain. However, when we correlated the duration of the procedure with pain scores, we found no correlation between them (r=0.139). We think that the long duration as reported in the
placebo group might be a consequence of pain. In patients suffering from pain or cramps 
during the procedure, the clinician was moving the instruments slowly and sometimes he 
stopped the procedure for seconds till the patient return calm.

It is interesting that the baseline mean VAS score of anticipated pain before the OH 
was 1 in almost all cases. Perhaps this could be confounded by the received medications 
and the pre-inclusion counseling that OH is relatively easy and short procedure. 
Moreover, pain perception could be affected by biological, psychological, social factors, 
study expectations, individual characteristics and previous therapeutic experiences of the 
patients [27,28].

Women in HBB group reported more side effects than other groups. Therefore, 
diclofenac potassium is more suitable for use in pain relief due to its lower rate of adverse 
effects. Tam and Yuen previously reported in their study one woman developed drug rash 
and one complained of epigastric pain with the use of diclofenac sodium [19].

Paulo and his colleagues reported in their systematic review that the use of mini-
hysteroscopy is less painful and more acceptable than the traditional hysteroscope (5 mm 
scopes) [29]. However, in their recent meta-analysis they found that mini-hysteroscopy is 
still painful and 30% of women may report high pain scores with its use [30]. They 
recommend continuing investigation on medications and techniques for pain relief during 
OH.

Our study had some strengths; it was a randomized double-blind controlled trial. A 
single gynecologist performed all the OH procedure and a single researcher interviewed 
the patients and collected the VAS score results to avoid any bias. We were able to 
recruit our calculated sample size for achieving sufficient power to detect a significant 
difference in our primary outcome. The main limitation of the study was the subjectivity in 
reporting pain through VAS score as there are no objective parameters to evaluate pain.

In conclusion, this study indicates the use of oral diclofenac potassium 1 hour 
before diagnostic OH could be an effective analgesic with easier and shorter duration of 
the procedure. HBB is another option but it is less effective than diclofenac potassium
with more adverse effects. Further trials on a larger sample size are warranted to confirm our results. Additionally, we recommend further studies evaluating the use of both medications in operative procedures.

Precis
Oral diclofenac potassium is more effective than hyoscine-N-butyl bromide in reducing pain perception in patients undergoing office hysteroscopy.

Acknowledgments: None.
Disclosures: None.
References:


Figure legend:

Figure 1: The study flowchart.

Enrollment

Assessed for eligibility (n=144)

* Declined participation (n=2)
* Excluded (n=13)
  - Cardio-pulmonary diseases (n=4)
  - Pelvic infection (n=3)
  - Allergy to NSAIDs (n=3)
  - Heavy vaginal bleeding (n=3)

Randomized (n=129)

Diclofenac potassium group (n=43)

Hyoscine-N-butyl bromide group (n=43)

Placebo group (n=43)

Follow-Up

- Mean pain score during OH
- Mean pain score immediately and 30 min after OH
- Ease of OH
- Duration of OH
- Adverse effects of medications

Analyzed (n=43)  Analyzed (n=43)  Analyzed (n=43)
Figure 2: The patients' vital signs before and after office hysteroscopy.

Figure 3: The mean pain scores of the study groups at all-time points.

Tables:

Table 1: The baseline characteristics of the study participants.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diclofenac group</th>
<th>HBB group</th>
<th>Placebo group</th>
<th>p-value</th>
</tr>
</thead>
</table>

P-value > 0.05 regarding all comparisons

SBP = Systolic blood pressure; DBP = Diastolic blood pressure; OH = Office hysteroscopy; HBB = Hyoscine butyl bromide
### Table 2: The study outcomes in all groups.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Diclofenac group (n = 43)</th>
<th>HBB group (n = 43)</th>
<th>Placebo group (n = 43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS before OH</td>
<td>1.00 ± 0.0</td>
<td>1.00 ± 0.0</td>
<td>1.09 ± 0.29</td>
<td>0.5</td>
</tr>
<tr>
<td>VAS during OH</td>
<td>2.12 ± 1.03 <em>z</em></td>
<td>3.02 ± 1.55</td>
<td>5.67 ± 1.82 *x,y</td>
<td>0.001*</td>
</tr>
<tr>
<td>VAS immediately after OH</td>
<td>1.23 ± 0.57 <em>z</em></td>
<td>1.56 ± 0.73</td>
<td>2.86 ± 1.39 *x,y</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

HBB; hyoscine-N-butyl bromide, CS; cesarean section, OH; office hysteroscopy

All variables are presented as mean ± standard deviation or frequency (%).
<table>
<thead>
<tr>
<th></th>
<th>Group A (diclofenac)</th>
<th>Group B (placebo)</th>
<th>Group C (HBB)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS 30 min after OH</td>
<td>1.05 ± 0.50</td>
<td>1.00 ± 0.0</td>
<td>1.19 ± 0.50</td>
<td>0.23</td>
</tr>
<tr>
<td>Ease score of OH</td>
<td>1.19 ± 0.50</td>
<td>1.19 ± 0.69</td>
<td>1.79 ± 1.16</td>
<td>0.001*</td>
</tr>
<tr>
<td>Duration of OH (min)</td>
<td>4.65 ± 0.97</td>
<td>5.23 ± 1.58</td>
<td>6.88 ± 2.35</td>
<td>0.01*</td>
</tr>
<tr>
<td>Need for additional analgesia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (7)&lt;sup&gt;z&lt;/sup&gt;</td>
<td>9 (20.9)</td>
<td>37 (86)&lt;sup&gt;x,y&lt;/sup&gt;</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

HBB; hyoscine-N-butyl bromide, OH; office hysteroscopy, VAS; visual analog scale

<sup>a</sup> Variables are presented as frequency (%)

<sup>*</sup> Statistical significant difference between all groups

<sup>x</sup> indicates statistical significance between diclofenac and placebo groups

<sup>y</sup> indicates statistical significance between HBB and placebo groups

<sup>z</sup> indicates statistical significance between diclofenac and HBB groups