Efficacy of oral celecoxib and hyoscine butyl-bromide versus placebo during copper intrauterine device placement in women delivered only by elective cesarean section: a randomized controlled study

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Keywords: Intrauterine device; celecoxib; hyoscine butyl-bromide; contraception; pain relief

Abstract

Objective: *To compare the efficacy and tolerability of celecoxib to hyoscine butyl bromide (HBB) and placebo in reducing pain scores during placement of copper intrauterine devices (IUD) in parous women who have undergone elective cesarean section and who have had no previous vaginal deliveries.*

Methods: *We conducted a randomized, double-blind, placebo-controlled trial at a tertiary University hospital from April 2018 to September 2018. The study included women who had never delivered vaginally and who desired copper IUD insertion. We randomized the study participants in a 1:1:1 ratio to celecoxib, HBB or placebo groups. They took the tablets orally two hours before IUD insertion. The study outcomes were the self-reported pain measurements, using a 10-cm Visual Analogue Scale (VAS), taken during tenaculum placement, sound insertion, IUD insertion and five minutes post-insertion, as well as an ease of insertion score.*

Results: *The study included 105 women (n=35 in each group). The baseline characteristics were similar among all groups. The mean pain score in the celecoxib group was lower during IUD insertion than placebo (1.97 vs 4.34, p<0.001). Moreover, the ease of insertion score was significantly better with celecoxib [1.56 vs. 3.03, p< 0.001] than with placebo. Similarly, Women in the HBB group were more likely to report lower pain scores during IUD insertion (2.91 vs 4.34, p<0.001) and lower ease of insertion score [1.43 vs. 3.03, p< 0.001].*

Conclusions: *The use of celecoxib and HBB may both reduce the pain associated with copper IUD insertion among women with no previous vaginal delivery. However, celecoxib is better tolerated with fewer side effects.*

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Introduction

The intrauterine device (IUD) is considered one of the most effective long-acting, reversible contraception (LARC) methods with a lower incidence of failure when compared with other reversible contraception methods. Despite its effectiveness, it is still an underutilized method of contraception in many countries.[1,2] This might be attributed to the pain associated with the insertion procedure.[3]

Several medications have been used to decrease pain during the procedure including the use of topical anesthesia, opioids, misoprostol, paracervical block and non-steroidal anti-inflammatory drugs (NSAIDs).[4-11] Various NSAIDs have been shown to decrease pain associated with copper IUD insertion, including studies on diclofenac, naproxen, indomethacin, ibuprofen, and ketorolac.[5,12-15] All these agents are non-selective cyclooxygenase-1 (COX-1) and COX-2 inhibitors with common gastrointestinal adverse effects.

Celecoxib is a relatively new selective COX-2 inhibitor. COX-1 has a role in the protection of the gastrointestinal mucosa, hemodynamics of the kidney, and platelet thrombogenesis, whereas COX-2 produces prostaglandins, which are triggered by inflammation and cause pain. Therefore, the use of COX-2 inhibitors leads to pain reduction with fewer of the gastrointestinal adverse effects that are relatively common with non-selective NSAIDs.[16]

Hyoscine butyl-bromide (HBB) is an antispasmodic drug used for relief of muscle spasms. Its main action on the pelviabdominal parasympathetic ganglia is through blocking the transmission of neural impulses and inhibiting cholinergic transmission in the synapses, thus relieving spasm in the smooth muscles of gastrointestinal, biliary, urinary and genital organs.[17] Moreover, previous studies have proven its effect on shortening the duration of labor due to its cervical spasmolytic action.[18,19]

Therefore, the current study aims to compare the effectiveness and side effects of oral celecoxib and HBB to placebo in decreasing pain associated with copper IUD placement among multiparous women delivered only by elective cesarean section.

Materials and Methods

Study type, setting, and duration

A randomized, double-blind, placebo-controlled (RTC) study was carried out at the Kasr Al-Ainy Family Planning Clinic, Cairo, Egypt between April 2018 and September 2018. This study was designed and reported according to the revised recommendations of ClinicalTrials.Gov for improving the quality of reporting RCTs (registered trial; NCT03499743). The institutional review board approved the study, and we obtained written informed consent from all participants before enrollment in the study.

Study participants

We invited all women who attended the Family Planning Clinic requesting an IUD placement during the study period to participate in the study. We included women with the following inclusion criteria: multiparous, delivered by elective cesarean section (CS), aged 18-49 years, and who did not take any analgesics, sedatives or misoprostol in

the 24 hours before insertion. We excluded women who were not eligible for IUD placement according to World Health Organization (WHO) eligibility criteria.[20] Additionally, we excluded women with suspected pregnancy, history of dysmenorrhea, those who presented for IUD removal and reinsertion, women with a neurological illness that results in altered pain sensation and, finally, those with allergy or contraindication to HBB.

Sample size

Validity considerations for this study were based on work by Abbas, et. al.[21] in their study of diclofenac (assumed to be similar to celecoxib) for pain relief during IUD insertion in hopes of matching or beating their VAS values for mean±SD of 3.66± 0.87. We hypothesized that HBB would be at least as effective as celecoxib in pain reduction. Pain ratings with a difference of 2 cm along the 10 cm VAS used for this study determined to show a clinically significant difference between study groups.[8]

Accordingly, the minimum sample size was 35 participants in each arm to be able to reject the null hypothesis with 80% power at $\alpha = 0.05$ level using a one-way analysis of variance test. Sample size validity calculation was done using *G*Power* software *version 3.1.2* for *MS* Windows, Franz Faul, Kiel University, Germany.

Allocation

Eligible participants were randomly divided into three equal groups. We used a double dummy technique to ensure blinding. Group (I) women received celecoxib 200 mg (Celebrex® 200 mg, Pfizer, USA) plus a placebo tablet similar in shape and size to HBB. Group (II) women received HBB 10 mg (Buscopan® 10 mg, Sanofi-Aventis Ireland Ltd. Dublin, Ireland) plus a placebo tablet similar in shape and size to celecoxib. Group (III) women received two placebo tablets, one each of similar color, shape and size for both HBB and celecoxib. Placebo tablets were manufactured in the Department of Pharmaceuticals, Faculty of Pharmacy, Cairo University. All tablets were taken under the supervision of one of the study investigators orally two hours before IUD insertion. The pharmacy dispensed the study medications based on the randomization scheme to ensure allocation concealment. A single pharmacist was involved in the packaging of all medications into sterile boxes with labeling them as 1, 2 and 3.

Randomization

A statistician, not otherwise engaged in the study, prepared a computer-generated random table and placed the allocation data in serially numbered sealed opaque envelopes. Each envelope had a card noting the group identifier inside. The key for the allocation of identifying serial numbers to members of each group was kept until the end of the study by the statistician. The investigators responsible for IUD placement and data collection were blinded to group allocations. In addition, both the patients and the statistician who did the final data analysis were blinded to group allocations. Once the allocation had been made, it could not be changed.

Study intervention

Prior to placement of IUDs, baseline data, including a complete evaluation of patient history as well as general,

abdominal and pelvic examination of all study participants was performed by the same study investigator. The same investigator also instructed the participants on the use of the standard10-cm VAS for pain scoring. A different study investigator, with ten years of experience in family planning services, inserted the IUD (ParaGard®T380A; Cooper surgical, USA, Inc. North Wales) for all participants using the standard technique of application prescribed by the manufacturer. IUD insertion was performed while women were menstruating. The day of the menstrual cycle ranged from the first to the fifth.

To insert the IUD, a speculum was placed into the vagina and the cervix was cleansed with povidone-iodine. Then, the anterior lip of the cervix was grasped with a single toothed vulsellum tenaculum for fixation of the uterus, and a metal uterine sound was inserted for measurement of uterine length, followed by IUD insertion. This standard Copper IUD placement technique was used for all participants without the aid of ultrasound guidance. Any complications, such as tenaculum site bleeding, uterine perforation and failure of insertion were recorded when and if they occured.

During the procedure, the patient's pain perception was assessed using VAS graded from zero to 10 with zero corresponding to no pain and 10 corresponding to the worst possible pain. A study investigator was standing beside the patient during IUD placement with copies of the 10-point VAS printed on multiple sheets of paper. The patient was asked to mark her level of pain on a copy of the VAS at four points during the procedure: during tenaculum placement, during sound insertion, at time of IUD placement and five minutes after the end of placement.

After placement, the investigator who inserted the IUD evaluated the ease of insertion score (ES) using a graduated VAS-like scale from zero to 10; on which 10 meant a terribly difficult procedure and zero meant a very easy procedure.[8] Patients were asked by the investigator if they needed additional analgesia at 15 minutes after IUD placement. Finally, patients were asked to report any adverse reactions experienced after the intake of the study medications through an open-ended question about medication side effects.

Statistical analysis

Data coding and data entry were done using the statistical package SPSS (Statistical Package for the Social Sciences) version 22 (Armonk, NY: IBM Corp). Data were summarized as mean and standard deviation for quantitative data and as frequency and percentage for categorical data. The differences (MD) between any two groups was reported as a mean and its corresponding 95% confidence interval. Comparisons between quantitative variables were made using non-parametric Kruskal-Wallis and Mann-Whitney tests. For comparing categorical data, Chi-square (X^2) tests were performed. P-values less than 0.05 were considered as statistically significant.

Results

At enrollment, 145 women were eligible for inclusion in our study; however, a total of 105 actually participated. Of those eligible for inclusion, 25 chose not to participate, while 15 potential participants were ineligible as they had

been delivered by emergency CS. The remaining 105 participants were randomly allocated to groups for a total of 35 per group (Figure 1).

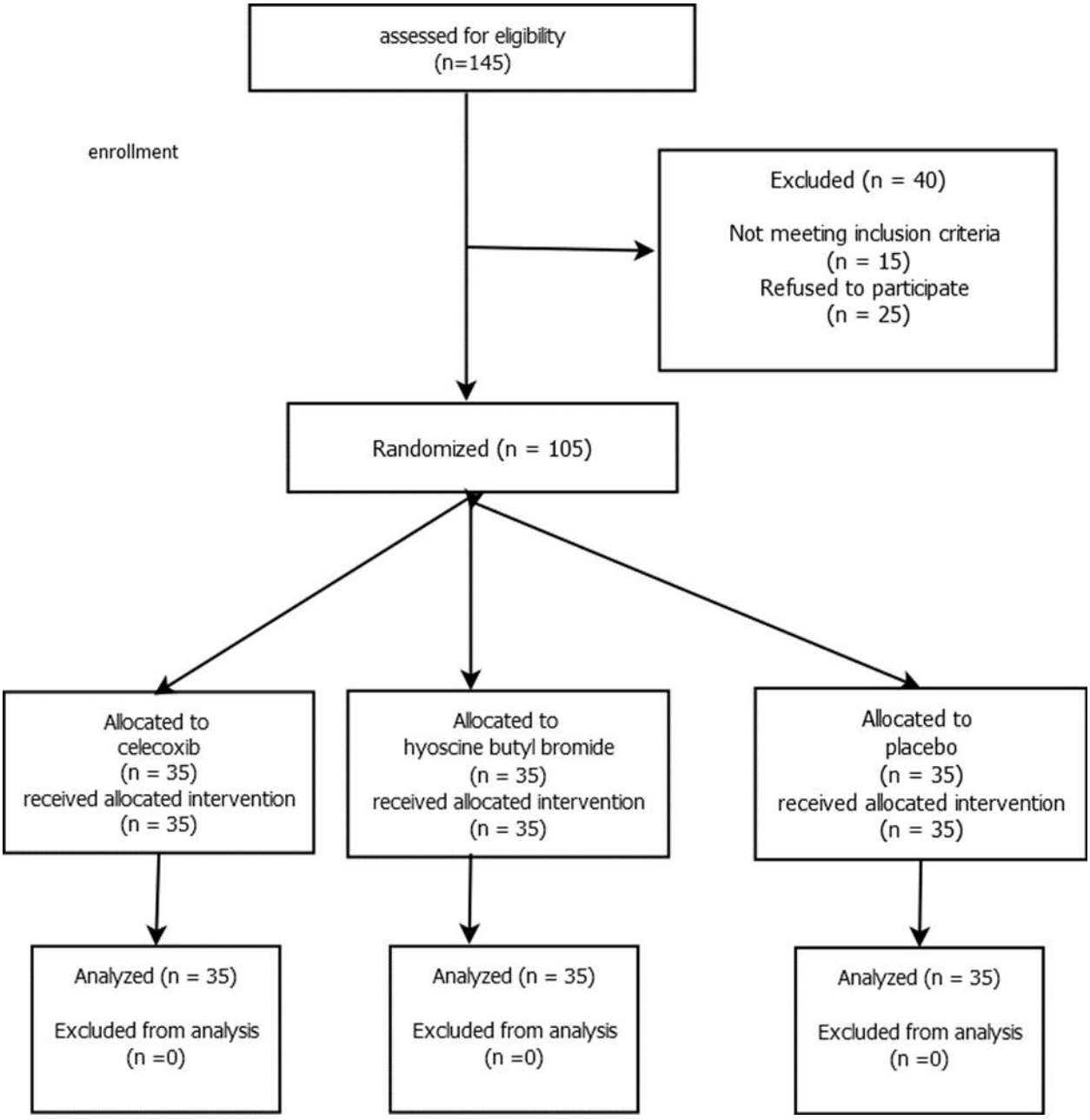

Figure1. Flowchart of the study participants.

Study outcomes

The primary outcome of the study was

the mean value of VAS scores during IUD placement across the study groups. Secondary outcomes included the mean VAS score at various other stages during the insertion procedure, the mean of the physician-determined score for ease of IUD insertion, the duration of the placement procedure, the rate of need for additional analgesia and the side effects of the study medications.

The baseline characteristics of the study participants are illustrated in Table 1 and showed that there was no statistically significant difference across all three groups. A subgroup study, comparing pain scores from lactating and non-lactating, placebo users found no difference between the groups (p=0.413)

Table 1: The baseline characteristics of the women according to the medication used prior to IUD insertion

Characteristics	Celecoxib group (N= 35)	HBB group (N= 35)	Placebo group (N= 35)	P-value
Age	28.37±6.48	29.49±6.93	29.09±7.18	0.825
Gravidity	3.03±1.81	2.83±1.15	3.11±1.25	0.456
Parity	2.49±1.27	2.37±1.09	2.66±1.21	0.530
BMI	31.40±6.91	29.29±5.86	30.66±5.05	0.283
Education				0.716
Primary	24(68.6%)	25(71.4%)	27(77.1%)	
High	11 (31.4%)	10 (28.6%)	8 (22.9%)	
Interval from last delivery				0.766
<6 months	16(45.7%)	17(48.6%)	19(54.3%)	
>6 months	19(54.3%)	18(51.4%)	16 (45.7%)	
Previous IUD insertion	14 (40.0%)	18 (51.4%)	17 (48.6%)	0.608
Lactational status				0.631
Lactating	21 (60.0%)	19 (54.3%)	17 (48.6%)	
Not lactating	14 (40.0%)	16 (45.7%)	18 (51.4%)	

HBB; hyoscine butyl bromide, BMI; body mass index, IUD; intrauterine device

In this study, VAS pain scores showed significant differences for tenaculum placement, sound insertion and IUD insertion as well as for ease of insertion (p<0.001 for all). However, differences were not statistically significant with regard to the duration of insertion, the need for additional analgesia and tenaculum site bleeding across all groups (p=0.460, p=0.179 and p=0.183, respectively) (Table 2). No member of any group needed cervical dilatation for IUD insertion.

Table 2: The study outcomes during IUD insertion according to the medication used prior to the procedure.

Study Outcomes	Celecoxib group (N= 35)	HBB group (N= 35)	Placebo group (N= 35)	P-value
VAS tenaculum placement, cm	2.24±0.99	2.30±0.95	3.83±1.02	< 0.001
VAS sound insertion, cm	1.88±1.12	2.23±0.73	4.14±0.73	< 0.001
VAS IUD insertion, cm	1.97±1.03	2.91± 0.82	4.34±0.87	< 0.001
VAS 5 minutes post-insertion, cm	1.06±0.89	1.23±0.69	2.86±0.77	< 0.001
Ease of insertion score, cm	1.56±0.61	1.43±0.78	3.03±1.29	< 0.001
Duration of insertion, sec	56.79± 8.35	55.83±11.48	54.40±10.74	0.460
Failure of insertion	0	0	0	------
Perforation	0	0	0	------
Need for additional analgesia	3 (8.8)	4 (11.4)	3 (8.8)	0.179
Tenaculum site bleeding	3 (8.8)	4 (11.4)	4 (11.4)	0.183

HBB; hyoscine butyl bromide, VAS; visual analog scale, IUD; intrauterine device
Data are presented as the absolute mean± standard deviation or n (%)

When compared with women taking placebo, women in the celecoxib group had significantly lower pain during tenaculum placement [mean difference (MD)=1.59, 95% confidence interval (CI): 1.06-2.12, p<0.001], sound placement [MD= 2.26, 95% CI: 2.61 - 7.13, p< 0.001], IUD insertion [MD= 2.37, 95% CI: 0,39-4.35, p< 0.001] and five minutes post-insertion [MD =1.8, 95% CI: 0.3-3.3, p< 0.001] with greater ease of insertion score [MD= 1.47, 95% CI: 0.7-9.94, p< 0.001].

Although differences between study groups were not large, they were significant. For example, women in the celecoxib group were also more likely to report lower overall pain scores during IUD insertion (1.97 vs 4.34, p<0.001). The same was observed with pain scores during speculum placement, tenaculum placement and sound insertion (p<0.001). There was also a decrease in pain scores at five minutes after IUD insertion (1.06 vs. 2.86, p<0.001) (Table 2). Although the difference between both groups was statistically significant, no clinically significant difference was found as the MD was less than 2 cm.

Similarly, women in the HBB group had significantly lower tenaculum pain when compared with placebo during IUD placement [MD=1.53, 95%CI: 0.66-2.4, p< 0.001], IUD placement [MD= 1.43, 95% CI: 0,8-2.65, p< 0.001]; sound placement [MD= 1.91, 95% CI: 1.89 – 1.93, p< 0.001], and five minutes post-insertion [MD= 1.63, 95% CI: 0.63-2.63, p< 0.001] as well as lower (easier) ease of insertion scores [MD= 1.60, 95% CI: 0.4.75 - 7.95), p< 0.001]. Furthermore, women in HBB group were more likely to report lower overall pain scores during IUD insertion (2.91 vs 4.34, p<0.001).

Moreover, pain scores during speculum placement, tenaculum placement and sound insertion were significantly lower (p<0.001). There was also a decrease in pain scores at five minutes after IUD insertion (1.23 vs. 2.86, p<0.001) (Table 2). However, the difference between these groups was not clinically significant.

Women in the celecoxib group had tenaculum pain scores that were similar to those for patients receiving HBB during IUD placement [MD =0.06, 95% CI:-0.38-5, p=1.00], IUD placement pain [MD= 0.94, 95%CI:-0.13-0.50, p= 0.05], sound placement [MD= 0.35, 95%CI:-4.44-5.14, p=0.641], five minutes post-insertion [MD= 0.17, 95%CI-2.23-2.57), p= 1.000]; ease of insertion score [MD= 0.13, 95%CI: -2,01-2.27 , p= 1.00].

Complications and side effects had little impact on outcomes for this study. In all groups, none of the procedures resulted in perforation. None of the women who received celecoxib had nausea, but six patient who received HBB and three women in the placebo group suffered from nausea (p=0.039) after IUD insertion. None of the women who received placebo had dryness of mouth versus one in the celecoxib group, and six in the HBB group (p=0.016). None of the women who received placebo had dizziness versus three in the celecoxib group and four in the HBB group (p=0.157).

Discussion

One of the main barriers for IUD use is the fear of pain experienced during insertion. Therefore, improved pain control during insertion could enhance IUD use and decrease the rate of unplanned pregnancies.2 To the best of our knowledge, this is the first trial to study oral celecoxib (a selective COX-2 inhibitor) and HBB to reduce pain associated with copper IUD placement. Our VAS results show that HBB (100 mg) and oral celecoxib (100 mg) significantly decreased the pain during tenaculum placement, sound placement, IUD placement and five minutes post-insertion, and increased ease of insertion scores, as compared with placebo. No significant difference in the mean pain scores was observed between HBB and celecoxib during any step of IUD placement.

Several RCTs have studied the use of various analgesics for reducing pain associated with IUD placement. Abbas et al. reported that the use of oral diclofenac potassium slightly reduced pain during tenaculum application and IUD placement. However, when comparing diclofenac potassium with HBB, Abbas found oral diclofenac potassium was more effective.[21] Also, Fouda et al. reported that the use of oral diclofenac potassium combined with lidocaine gel slightly induced pain reduction during tenaculum application and IUD placement.[5] Bednarek et al. compared Ibuprofen 800 mg with placebo during IUD placement, but they reported no reduction of pain associated with its use.[12]

On the other hand, one randomized controlled trial of 103 women found that either 550 mg of naproxen or 50 mg of tramadol one hour before IUD placement in multiparous women reduced procedure pain as compared with placebo. Mean pain scores were 2.3 in the tramadol group, 2.9 in the naproxen group and 4.9 in the control group. Tramadol was statistically superior to naproxen, and both were statistically

superior to the placebo.[22]

In a pilot RCT, intramuscular ketorolac 30 mg given 30 minutes before the procedure was found to be superior to saline for IUD placement pain (5.8 vs. 8.2, p< 0.02).[10] Another study showed that giving oral ketorolac 40-60 minutes before IUD placement is effective in reducing pain overall pain, pain during IUD insertion, and pain 10 minutes post-procedure.[23] However, this same effect was not detected in the 51 multiparous women who were part of the trial, although multiparous women in the ketorolac arm had less pain at both 5 and 15 minutes after the procedure.

We could find no report on the use of celecoxib or any other non-selective COX 2 inhibitor during IUD placement. Celecoxib has shown greater effectiveness than tramadol before hysteroscopy in reducing pain evoked by the procedure. Furthermore, celecoxib is better tolerated with no reported side effects.[24]

In our own study, side effects, including nausea and dryness of the mouth were rarely reported among women in the celecoxib group as compared to those in the HBB group. Celecoxib, as a selective COX-2 inhibitor, is less likely to cause the side effects of non-selective NSAIDs and opioids. Although there has been concern over the risk of major cardiovascular events (non-fatal myocardial infarction and stroke), the risk with selective COX-2 inhibitors was found to be dose-dependent and similar to that of most non-selective NSAIDs.[25]

The key strength of our study is the randomized design. We were able to recruit the calculated sample size for achieving adequate power to detect a clinically significant difference in VAS scores. Additionally, the study was conducted at the same clinic, with a single, experienced investigator performing IUD insertion to avoid any inter-assessor variation in VAS score evaluation.

The main limitation of the study is the subjectivity in reporting pain through VAS scores. However, it is a widely accepted method, and there are currently no other objective parameters for evaluating pain. Another limitation that may affect the generalizability of the study is that we tested both drugs only during placement of a copper IUD. Finally, a substantial proportion of our study participants were breastfeeding, which is known to mask pain during IUD placement. This confounding factor may also be a limitation to this study.

In conclusion, the use of celecoxib and HBB reduce the pain associated with copper IUD placement in women with no previous vaginal delivery. We need to carry out further RCTs with a larger sample size to confirm these findings.

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