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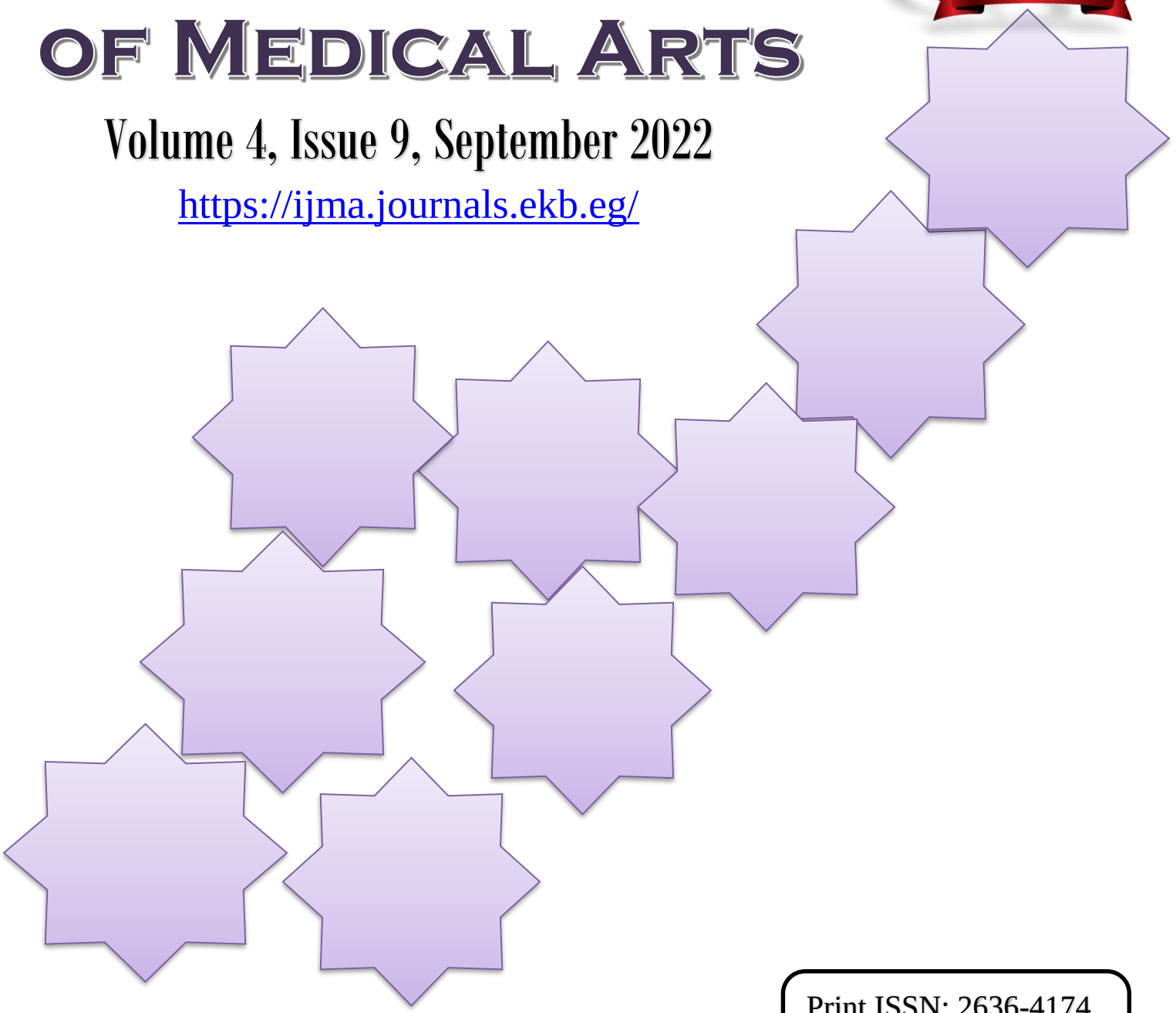

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Intravenous Diclofenac Sodium Versus Ibuprofen as A Component of Multimodal Post-Operative Analgesic Plan After Caesarean Section: A Double-Blinded Randomised Comparative Study

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ABSTRACT

Background: Postoperative pain has a significant direct relationship to morbidity of female patients after caesarean section. Adequate post caesarean section pain management is fundamental.

Objectives: To compare the postoperative analgesic effect of both ibuprofen and diclofenac sodium on pain score, rescue opioid requirement and patient satisfaction in female patients after caesarean section.

Patients and methods: This prospective, randomised, double-blind comparative study was conducted over a period of eight months in Kafr Elsheikh University Hospital, obstetric unit. The study included any American Society of Anaesthesiologists [ASA] physical status II female patients aged 18–40 years who were scheduled for elective and emergency caesarean section under spinal anaesthesia. Patients were randomly allotted into two groups: Group D [intravenous diclofenac group] and Group I [intravenous ibuprofen group].

Results: First request of analgesics, total opioid consumption and VAS showed no significant differences between two groups except after 4hours and 8 hours postoperatively which showed significant decrease in diclofenac group than ibuprofen group. Also patient satisfaction was higher in Diclofenac group. There was increase in bleeding tendency [APTT, BT, and HB results] and abnormal abdominal bleeding attacks in diclofenac group.

Conclusion: Diclofenac decreases postoperative pain with higher potency than ibuprofen but unfortunately with more tendency to gastrointestinal complications and bleeding tendency.

Keywords: Postoperative; Pain management; Caesarian section; Bleeding.

INTRODUCTION

Postoperative pain can share significantly to morbidity of female patients after caesarean section if not treated adequately by delaying the patients' recovery and delaying ability to return to normal daily functional activities with many psychological and physiological complications [1]. Inadequately treated post-operative pain may lead to chronic pain syndrome. So, adequately treated post caesarean section pain is mandatory to facilitate mothers' early mobilisation, so preventing thromboembolic complications and allowing early breast feeding [2].

During caesarean section procedure, there is extensive tissue dissection and organ handling which release large amount of pain mediators. Pain after caesarean section originates mainly from deep visceral organs. Meanwhile, surgical wounds are another source of somatic pain. A multimodal pain management plan should be employed to act on both components of pain. Peripheral nerve blocks like quadratus lamborum and TAP block provide reasonable analgesic management of somatic pain, sparing visceral pain. In order to overcome this limitation, a supplementary different parenteral analgesic like paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs], opioids and gabapentin can be used [3]. Opioids are better avoided because of their known adverse effects as it can cross the placenta and can cause dizziness, nausea, vomiting and respiratory centre depression [4].

NSAIDs are effective for treatment of postoperative pain [5]. Most NSAIDs act mainly by inhibiting the enzyme cyclooxygenase [COX], so preventing local prostaglandin synthesis [6].

One of the most commonly used NSAIDs is ibuprofen, which is used as adjuvant post-operative pain-killer. Diclofenac sodium is another NSAID that has been used widely in Rheumatology, as it has the benefits of a good efficacy and tolerability [7]. The mechanism of anti-inflammatory effects of ibuprofen is by inhibition of the activity of COX enzyme, which is important in the synthesis of prostaglandins [8]. These prostaglandins on one hand stimulate inflammatory processes which is one of its bad effects, and on the other hand these prostaglandins help vasodilatation and glomerular filtration which are some of its beneficial effects [9].

Diclofenac also act by the same mechanism as ibuprofen by blocking the COX enzymes which stimulate the formation of prostaglandins in the body which are overproduced in the sites of injury or harm causing inflammation and pain. By blocking the influence of COX enzymes, minute amount of prostaglandins is formed causing less pain and inflammation [10].

Although the efficacy of diclofenac and oral ibuprofen has already been well documented in head-to head RCTs [11], no study has specifically examined the safety, tolerability and efficacy of intravenous form of both diclofenac and ibuprofen together. Several meta-analyses have examined the safety and tolerability of NSAIDs, however, these studies included oral formula of several other non-specific NSAIDs and anti-inflammatory drugs with different mechanism of action like selective COX-2 inhibitors [12-14]. We assume that intravenous ibuprofen has equivalent postoperative analgesic effect equal to diclofenac sodium with less unwanted effect on coagulation process as well as less bleeding episodes after surgery

THE AIM OF THE WORK

The primary aim is to compare the postoperative analgesic effect of both ibuprofen and diclofenac sodium on pain score, rescue opioid requirement and patient satisfaction in female patients after caesarean section. The secondary outcome is to compare the associated side effects caused by both medications mainly on bleeding and coagulation profile.

PATIENTS AND METHODS

This prospective, randomised, double-blind comparative study was conducted over a period of eight months in Kafr Elsheikh University Hospital, obstetric unit starting from February 2022. An approval from Kafr Elsheikh University with code [MKSU 50-6-4], Faculty of Medicine Institutional Ethics Committee was obtained before starting this study. The study included any American Society of Anaesthesio-logists [ASA] physical status II female patients aged 18–40 years who were prepared for elective and emergency caesarean section under spinal anaesthesia. All patients gave an informed consent before joining this study. Exclusion criteria included any patients had a history of severe medical conditions such as severe eclampsia and pre-eclampsia, drug hypersensitivity, local anaesthetic toxicity,

contraindications to regional anaesthesia [peripheral neuropathy and infection at the site of block], and patients with intraoperative complications like postpartum haemorrhage and severe foetal distress, any coagulation or GIT medical problems. Patients were randomly allotted into two groups: **Group D** [intravenous diclofenac group] and **Group I** [intravenous Ibuprofen group]. Randomisation was done using computer-generated sequence of random numbers in 1:1 ratio. Allocation concealment was done using sequentially numbered opaque sealed envelopes technique. A thorough preoperative assessment was done before the surgery.

Numerical rating scale [NRS] scale was explained to all patients preoperatively, we depended on it to measure post-operative pain severity. Patients were given premedication in form of intravenous ranitidine 50 mg and intravenous ondansetron 4 mg in the pre-operative period after confirmation of fasting status. Patients were delivered to operation theatre, identified and multichannel monitors which included pulse oximeter, electrocardio-graphy, non-invasive blood pressure and heart rate were attached and baseline values were obtained.

Spinal anaesthesia was given. Lumbar puncture was performed under aseptic conditions, at L3–L4 interspace through midline approach in sitting position using a disposable 25 Gauge Quincke's spinal needle. 2.5 ml of hyperbaric bupivacaine [0.5%] were injected in the subarachnoid space and patient was in supine position. 15° wedge pillow was placed under her right hip. The sensory block was evaluated along the mid-clavicular line bilaterally by pin prick method. The motor block was assessed according to the modified Bromage scale. Surgical incision was allowed after achieving a sensory level of anaesthesia up to T4 and Bromage block of scale two. Under all aseptic precautions TAP block was performed in both the groups; ropivacaine 0.75% [1.5 mg/kg diluted in 0.9% normal saline] 20 ml volume were injected on each side. Patients in Group D were given intravenous diclofenac sodium aqueous 75 mg after delivery of the baby and every 8 hours during the first 48 hours after surgery [15]. Similarly, Patients in Group I were given intravenous Ibuprofen 400 mg after delivery of the baby and every 8 hours during the first 48 hours after surgery [16].

Patients were observed for 30 min and then shifted to post-anaesthesia care unit. Pain severity was assessed by an investigator blinded to the allotment every 2 hours for the first 8 hours and then every 8 hours for the rest of 48 hours. Pain was measured using numerical rating scale [NRS] [0 = no pain and 10 = the worst possible pain]. Rescue analgesia was given to patients on demand or when NRS was more than 4 in the form of intravenous morphine 2mg each.

The following parameters were studied and compared: NRS at the studied intervals, the first request for analgesic and total opioid requirement in 48 hours after surgery. Patient satisfaction evaluation about degree of pain was performed at 48 h after the block. Patients were asked verbally to provide a score between 1 and 10 [0—not satisfied, 10—fully satisfied] depending on level of satisfaction achieved in pain relief. Coagulation profile [full blood count Prothrombin time [9-12.5 seconds] for evaluation of extrinsic coagulation pathway, activated partial thromboplastin time [22.1-30.9 seconds] for evaluation of intrinsic coagulation pathway, bleeding time [4-7 minutes] for evaluation of platelet function] were done preoperatively and 24, 48 hours after surgery to detect any drug related coagulopathy. Any abnormal bleeding attacks were also recorded and defined as any postoperative bleeding that required re-exploration of the wound.

Sample size: Sample size was calculated using G power program based on pain score values obtained from ***Martinez et al*.** [14] with power [1-β] of 80%, confidence interval of 95%. The results came back as 27 in each arm.

Statistics: The collected data were analysed using SPSS program [software version 20. Shapiro-Wilk test will be used to check the normality of the data distribution in continuous variables. For parametric quantitative data, descriptive statistics were done by mean+ [SD] or median with minimum & maximum of the range. In categorical data number and percentage were used. To compare both groups, independent samples t-test and Mann Whitney test were used for parametric data, meanwhile for non-parametric quantitative data Fisher exact test was used to compare the studied groups. The level of significance was taken at [P value < 0.05].

RESULTS

Fifty-seven patients completed the study. One patient in group D and two in group I did not complete the study due to lack of postoperative data. There mean-age was 27.8 ± 6.5 for group A and 29.0 ± 5.0 for group B [table 1].

Total-opioid recorded no significance in the differences between the mean of group D [53.0 ± 19.8] and that of group I [65.3 ± 24.1]. Patient satisfaction recorded a significant difference [p = 0.013] between group D that recorded the higher mean [8.9 ± 1.0] and group I that recorded the lower mean [8.2 ± 1.2] [table 2].

According to the first PT [PT1] the patients recorded mean of 11.8 ± 1.5 for group D and the higher one was equal 12.1 ± 1.5 for group I. Meanwhile, PT2 recorded 12.2 ± 1.4 and 12.9 ± 1.6, respectively. Also, PT3 recorded 12.0 ± 1.3 and 12.6 ± 1.4, respectively. Statistically, all PTs give no statistical differences between each couple [p > 0.05]. For APTT, the first [APTT1] recorded mean equal 25.7 ± 1.8 for group D and 25.2 ± 1.9 for the group I. The APTT2 showed means equal 29.5 ± 3.3 and 30.0 ± 3.1 for both groups, respectively, and the third time [APTT3] recorded means of 27.5 ± 2.0 and 28.4 ± 1.9 for both groups respectively. Statistically, all APTTs give no statistical differences between each couple [p > 0.05]. According to BT, the higher mean of BT1 was 5.7 ± 1.6 for group I while the lower one was 5.5 ± 1.3 for group D. Also, group D recorded the higher mean at BT2 [8.1 ± 1.6] while the lower result [7.7 ± 2.0] recorded with group I. However, the reverse was recorded with BT3; when group D recorded the lower mean [6.5 ± 1.6] and group I recorded the higher one [7.2 ± 1.6]. Statistically, all BTs give no statistical differences between each couple [p > 0.05] [table 3].

Data of HB at the first time [HB1] showed that the lower mean [114.5 ± 5.8] was recorded in group A while the higher one [117.0 ± 6.6] was belonging to the second group. The same trends were observed with HB2 [108.4 ± 6.1 and 109.8 ± 6.5, respectively] and HB3 [106.7 ± 5.6 and 107.8 ± 6.4, respectively]. Statistically, all HBs give no statistical differences between each couple [p > 0.05]. The incidence of post caesarean section bleeding was statistically insignificant in both groups [table 4].

Numerical rating scale showed the following results with no significant differences between the two groups [p > 0.05] except for the NRS 4 and NRS 8. NRS 4 showed the lower measurement of pain for group D [2.3 ± 0.5] while the higher one [2.6 ± 0.5] was obtained with the other group. Notably, there was a significant difference between these two groups [p = 0.024]. NRS 8 showed high significant difference between the two groups [p = 0.007] when group D recorded the lower mean for group D [3.0 ± 0.8] and group I recorded the higher [3.8 ± 1.1]. NRS 2 showed the lower measurement of pain for group D [2.8 ± 0.7] while group I recorded the higher one [3.0 ± 0.6] [table 5].

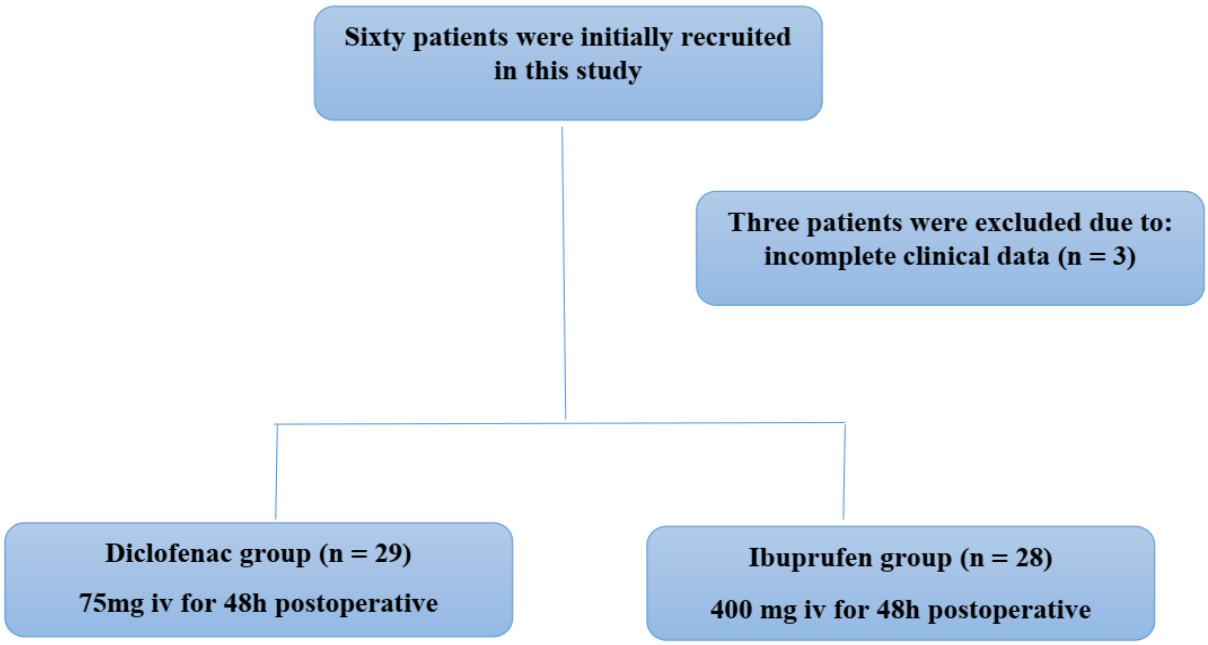

Figure [1]: CONSORT flowchart

Table [1]: Demographic and operative data of the studied groups

	Group D	Group I	P value
Age [years]	27.8 ± 6.5	29.0 5.0	0.424
Height [cm]	163 ± 14	160 ± 17	0.517
Weight [Kg]	82.7 ± 19.2	84.5 ± 16.8	0.389
Duration of surgery [min]	77.1 ± 10.2	73.2 ± 12.1	0.193

Table [2]: post-operative data

	Group D	Group I	P value
Total opioid consumption [mg]	53.0 ± 19.8	65.3 ± 24.1	0.318
Patient satisfaction	8.9 ± 1.0	8.2 ± 1.2	**0.013***

*: significant

Table [3]: Prothrombin time [seconds], activated partial thromboplastin time [seconds] and bleeding time [minutes] data of the studied groups

	Group D	Group I	P value
PT1 [immediate post-op]	11.8 ± 1.50	12.1 ± 1.48	0.489
PT2 [24h post-op]	12.2 ± 1.4	12.9 ± 1.6	0.116
PT3 [48h post-op]	12.0 ± 1.3	12.6 ± 1.4	0.119
APTT1 [immediate post-op]	25.7 ± 1.8	25.2 ± 1.9	0.313
APTT2 [24h post-op]	29.5 ± 3.3	20.0 ± 3.1	0.563
APTT3 [48h post-op]	27.5 ± 2.0	28.4 ± 1.9	0.071
BT1 [immediate post-op]	5.7 ± 1.6	5.5 ± 1.3	0.531
BT2 [24h post-op]	8.1 ± 1.6	7.7 ± 2	0.418
BT3 [48h post-op]	6.5 ± 1.58	7.2 ± 1.55	0.136

PT: Prothrombin time, APTT: Activated partial thromboplastin time, BT: Bleeding time

Table [4]: Haemoglobin level [gm/L] and number of abnormal bleeding episodes of the studied groups

	Group D	Group I	P value
HB1 (immediate post-op)	114.5 ± 5.8	117.0 ± 6.6	0.138
HB2 (24 h post-op)	108.4 ± 6.1	109 ± 6.5	0.413
HB3 (48 h post-op)	106.1 ± 5.6	107.8 ± 6.4	0.505
Abdominal bleeding 24	28/1	28/0	0.162

HB; Hemoglobin

Table [5]: Numerical rating scale [NRS] of the studied groups

	Group D	Group I	P value
VAS 2	2.8 ± 0.7	3.0 ± 0.6	0.230
VAS 4	2.3 ± 0.5	2.6 ± 0.5	**0.024***
VAS 6	2.8 ± 0.8	3.4 ± 1.1	0.051
VAS 8	3.0 ± 0.8	3.8 ± 1.1	**0.007***
VAS 10	2.4 ± 0.5	2.4 ± 0.5	0.912
VAS 12	1.5 ± 0.5	1.7 ± 0.5	0.139
VAS 18	1.5 ± 0.5	1.6 ± 0.6	0.707
VAS 24	2.5 ± 0.5	2.5 ± 0.5	0.891
VAS 30	1.4 ± 0.5	1.4 ± 0.5	0.678
VAS 36	1.6 ± 0.5	1.6 ± 0.5	0.912
VAS 42	2.3 ± 0.5	2.5 ± 0.5	0.367
VAS 48	1.4 ± 0.5	1.4 ± 0.5	0.883

VAS: Visual Analogue Scale, *: significant

DISCUSSION

We conducted this prospective, randomized, double-blind comparative study to compare the effectiveness of these preparations as post-operative analgesics. To the best of our knowledge, this is the first study which has compared the use of parenteral diclofenac sodium versus ibuprofen as a component of multimodal post-operative analgesic plan after caesarean section.

The mainstay of acute pain treatment in the inpatient setting are opioid analgesics [17] but they don't provide benefits to the underlying pathophysiology of the process of pain and inflammation. So in combination with opioids NSAID should be used as adjuvant agents for treatment of pain [18]. So the multimodal therapy and a preemptive analgesia approach is the golden standard treatment nowadays for moderate to severe acute postoperative, these combinations may help decreasing the total dose required from opioids decreasing their adverse effects side effects [19, 20].

The effects of diclofenac sodium on pain and inflammation not only caused by inhibition of COX enzyme decreasing PGs synthesis but also caused by inhibition of lipoxygenase enzymes and inhibition of thromboxane-prostanoid receptor, affecting arachidonic acid uptake and release and activation of the nitric oxide-cyclic guanosine monophosphate anti-nociceptive pathway [21].

Ibuprofen is a nonselective COX enzymes inhibitor and it is the most famous over-the-counter and prescribed NSAID in the world [22].

Patients of this study those were randomly allotted into two groups, Group D [intravenous diclofenac group] and Group I [intravenous Ibuprofen group].

In relation to age group and duration of surgery there were no statistical significant differences between two groups.

Our study showed also non-significant increase in bleeding tendency [APTT, BT, and HB results] in diclofenac sodium group in relation to ibuprofen Group. There was no significant difference in abnormal abdominal bleeding attacks in both groups. Bleeding tendency with the use of both drugs can be explained by the reversibly inhibiting platelet cyclooxygenase, thereby blocking formation of thromboxane A2. Effects of individual NSAIDs on platelet function, bleeding time, and clinical bleeding depend at least in part on dose, serum level, and drug half-life.

All NSAIDs are COX inhibitors, COX enzyme converts arachidonic acid in the cell membrane to prostaglandins, mediating fever, pain and inflammation. During this process, prostaglandin H2 is converted to five primary types of prostaglandins, including thromboxane A2 [which stimulates platelet aggregation and formation of blood clot] in platelets and prostacyclin [a vasodilator that preventing platelet aggregation] in the healthy endothelium [23]. Two types of COX enzyme are recognized they are [COX-1 and COX-2], COX-1 is constitutively expressed and is important for gastro protection from the acid in the stomach and in thromboxane formation by platelets. COX-2 is induced by inflammation in many tissues; however, it may also be constitutively expressed without inflammation as it contributes to renal physiology, bone resorption, reproductive function and neuro-transmission [24]. Inhibition rate of COX-1 to COX 2 of Ibuprofen is 2.5:1 which implies a low risk of bleeding or gastrointestinal problems, while diclofenac sodium has a ratio of COX-1 to COX-2 inhibition of 330:1 [25].

Dawn *et al.* [26] stated that continuous linear dose relationship between specific diclofenac doses and the risk of a serious gastrointestinal bleeding event and provides further support for guide- lines that recommend the use of NSAIDs at the lowest effective dose for the shortest duration.

Total opioid consumption and VAS showed no significant differences between two groups except VAS4 and VAS8 which showed significant decrease in diclofenac group than ibuprofen group also patient satisfaction recorded a significant increase in group D than recorded in group I.

Da Costa *et al.* [27] Stated that Diclofenac is the more potent than ibuprofen, so a smaller amount is needed compared to ibuprofen to produce similar results. Diclofenac is one of the strongest anti-inflammatory drugs.

Also, our study comes in correlation with a meta-analysis of 176 studies and 146,524 patients published in the Journal of Arthritis

Research and Therapy found that diclofenac 150 mg/day is more effective than ibuprofen 2,400 mg/day for arthritis pain relief [28].

This is due to the higher inhibition rate of diclofenac sodium than ibuprofen which makes more prostaglandin inhibition and more potency [25].

Conclusions: Our data point to the post-operative analgesic effect of intravenous diclofenac after caesarean section and comparing this effect to ibuprofen, also comparing their adverse effects as bleeding tendency and GIT bleeding. Diclofenac decreases postoperative pain with higher potency than ibuprofen but unfortunately with more tendency to gastrointestinal complications and bleeding so we recommend the use of gastric protective drugs with diclofenac to get the benefit and minimize the risk.

Conflict of interest: No conflict of interest.

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