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Comparative Clinical Study between Preoperative Oral Administration of Paracetamol, Celecoxib and Pregabalin on Postoperative Pain in Gynecological Laparoscope

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ABSTRACT

Background: Since the introduction of laparoscopic surgeries, postoperative pain has been generally reduced. However, it can still peak, especially during the early postoperative period and becomes the main cause of overnight hospital stay and prolonged convalescence after this day-case surgical procedure. Thus, optimizing postoperative pain relief, not only to sub-serve reduction of its intensity but to also enhance the recovery and shorten length of stay became the broader target of multimodal pain control regimens nowadays. That is why; searching for a drug that would be effective in reducing pain, safe from major adverse effects and can meanwhile possess an opioid-sparing potentiality would be a merit so as to improve the success rate of ambulatory day-care surgeries.

Objective: To study the analgesic effects of preemptive single oral dose of paracetamol, celecoxib and pregabalin in patients undergoing gynecological laparoscope.

Method: Preoperative evaluation, preparation and premedication was assessment, and routine laboratory investigations was done. **Postoperative pain, Level of Sedation was measured.**

Results: There was statistical significant difference between the three groups regarding VAS.

There was statistical significant difference between the three groups regarding the total pethidine consumption. Regarding postoperative level of sedation, blood glucose there was no statistical significant difference between the three groups.

Conclusion: Oral pregabalin in a dose of 150 mg 2 hour before surgery, is significantly attenuating pain intensity and total meperidine consumption during the first 6 hours postoperatively.

Keywords: Preoperative, Paracetamol, Celecoxib, Pregabalin, Postoperative Pain, Gynecological Laparoscope.

INTRODUCTION

Freedom from pain should be a basic human right, limited only by our knowledge, to achieve it [(1)]. Recent advances in the pathophysiology of pain have suggested thatit is possible to prevent or to attenuate the central neuralhyperexcitability that contributes to enhanced postoperative pain[(2)].

Local pain after laparoscopy will be associated with incisions for the operative ports. Lower abdominal pain may depend on the extent of intraperitoneal manipulation during diagnostic laparoscopy. Sterilization operations cause ischemia or damage to the fallopian tubes and are generally more painful than simple diagnostic procedures, with clips generally causing less pain than other techniques to occlude the tubes[(3)].

Upper abdominal, shoulder tip, and postural high back pain after laparoscopy are likely to be caused by gas retained in the peritoneal cavity. Carbon dioxide is usually used to expand the abdomen to allow surgical visualization. Although it is a soluble gas in comparison to oxygen and nitrogen, it can take up to two days to be absorbed from the peritoneal cavity. Pain from the residual gas is of delayed onset and may present once the patient has gone home. Hohlrieder *et al*. found that the worst pain after gynecological laparoscopic surgery was felt in the shoulder in 1% of the patients, two hours after surgery, but in 70% of the patients 24 hours after surgery[(3)].

Paracetamol (acetaminophen; N-acetyl-p-aminophenol) is well-absorbed from the proximal small bowel and is not subjected to significant first-pass metabolism in the liver, with oral bioavailability estimated between 63% and 89% in adults[(4)]. The minimum plasma paracetamol level required for analgesia and antipyresis is thought to be 10 μg/ml, and the therapeutic range is usually stated to be 10-20 μg/ml [(5)]. 150 μg/ml is considered to be the threshold for potential hepatotoxicity[(6)]. Peak plasma concentration (Cmax) is achieved approximately 45 min after 1g orally[(7)]. Paracetamol inhibits both isoforms of cyclooxygenase (COX); the constitutive COX-1 and the inducible COX-2. Paracetamol displays weak anti-inflammatory activity, few or no gastrointestinal side effects and only a small dose-dependent alteration of platelet function. Current evidence points to multisite activity in the central nervous system, involving inhibition of prostaglandin synthesis and interaction with both serotonergic and cannabinoid pathways [(8)].

Celecoxib is a tricyclic compound having a pyrazole ring that exhibits an excellent level of anti-inflammatory action against COX-2 enzymes [(9, 10)]. Celecoxib is a selective COX-2 inhibitor shown to be as effective as traditional NSAIDs as an analgesic for acute postoperative pain. Traditional NSAIDs inhibit both COX-1 and COX-2isoenzymes. Moreover,

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celecoxib has no effects on serum thromboxane and platelet functions, suggesting that it may be an effective postoperative analgesic [(11)]. Studies have suggested that the administration of selectiveCOX-2 inhibitors for preemptive, multimodal analgesia can improve postoperative pain and reduce the consumption of opioid analgesics. Celecoxib was rapidly absorbed and reached maximum concentrations by 1h.The absolute bioavailability of celecoxib was higher when given as a solution (64–88%) compared with capsule (22–40%). Celecoxib has fewer gastrointestinal side effects than traditional NSAIDs, such as diclofenac and ibuprofen [(12)].

Pregabalinis a structural analog of γ-aminobutyric acid, which shows the analgesic, anticonvulsant, and anxiolytic effects. In many countries, it is approved for the treatment of neuropathic pain [(13)]. Like gabapentin, it binds to the α-2-δsubunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters (including glutamate, norepinephrine, substance P, and calcitonin gene-related peptide) and blocking the development of hyperalgesia and central sensitization [(14)]. Pregabalin is more potent than the similar drug, gabapentin. It is rapidly absorbed orally with >90% bioavailability, achieves peak plasma levels within 30 min to 2 h. and shows linear pharmacokinetics.The most common adverse events are dizziness and somnolence, and pregabalin has no effect on arterial blood pressure or heart rate[(15)]. Laparoscopy was first performed about a century ago, but came into more routine practice around 50 years ago such as tubal ligation and liver biopsy.The rapid advances that have occurred in surgical procedures were developed by general surgeons. Cholecystectomy was first performed about 30 years ago. Using these techniques, gynecological laparoscopic surgery has developed recently, and is used for ovarian surgery such as (removal of an ectopic pregnancy, treatment of endometriosis, or ovarian cystectomy), laparoscopically-assisted vaginal hysterectomy (LAVH), and LAVH with radical hysterectomy. For diagnostic surgery, there is a clear reduction in operative trauma with laparoscopy compared to laparotomy. Other benefits of laparoscopic surgery include reduced hospital stay, as also improving cosmetic results and patient satisfaction [(16)].

AIM OF THE WORK

The aim of this work was to study the analgesic effects of preemptive single oral dose of paracetamol, celecoxib and pregabalin in patients undergoing gynecological laparoscope.

PATIENTS

After approval of Ethical Committee of Faculty of Medicine and written informed consent from patients, the present study was carried out in Al-Azhar University Hospitals on ninty patients, 18-40 years old, ASA physical status I or II of body mass index less than 30, scheduled for elective gynecological laparoscopyunder general anaesthesia.

Patients were randomly categorized into three equal groups (thirty each):

GroupI: Patients received paracetamol 1gm orally, 2 h before induction of anaesthesia with sips of water.**GroupII:** Patients received celecoxib 200mg orally, 2h before induction of anaesthesia with sips of water.**GroupIII:** Patients received pregabalin 150mg orally, 2h before induction of anaesthesia with sips of water.

METHODS

Preoperative evaluation, preparation and premedication was assessment, and routine laboratory investigations was done.

Postoperative pain:

Assessment of pain using a visual analogue scale (VAS) at the following times postoperative (every 30 min for 2 h, 4 h and after 6 h postoperatively), If VAS ≥3 patients were received intravascular meperidine.

Level of Sedation: It was assessed with the Ramsay sedation scale

Patients with a sedation scale of 2 or 3 were considered as sedated.

Patients were assessed at the following times postoperatively (every 30 min for 2 h, 4 h and after 6 h postoperatively).

Measuring blood glucose levels:

At the following times postoperative (every 30 min for 2 h, 4 h and after 6 h postoperatively) by using Glucose Assay Kit (ab65333) measures glucose in various biological samples.

Postoperative side effects:

Patients were observed for any side effects postoperatively during 6 hours in the ward such as nausea, vomiting,hurt burn, gastric upset, blurring of vision and excessive sedation.

Statistical method

The Data was collected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software.

Arthematic mean, standard deviation, for categorized parameters, chai square test was used while for numerical data t-test was used to compare two groups while for more than two groups ANOVA test was

used. To find the association between two variables, spearman correlation coefficient test was used The level of significant was 0.05.

RESULTS

Age in group I ranged from 19-30 with mean value 24.17±3.43, in group II ranged from 20-32 with mean value 25.40±3.89 and in group III ranged from 20-31 with mean value 25.17±3.07. BMI in group I ranged from 21.2-32 with mean value 26.30 ± 3.19, in group II ranged from 21-31.9 with mean value 26.26 ±2.88 and in group III ranged from 21.6-31.8 with mean value 26.68 ± 3.14. There was no statistical significant difference between the three groups regarding their demographic data (P > 0.05).

Table (1) shows comparison between the three groups regarding HR. There was statistical significant difference between group I and II at all period (P1 < 0.05). There was statistical significant difference between group I and III at all period (P2 < 0.05). There was no statistical significant difference between group II and III (P3 >0.05) except period 0 and 60 min (P3 < 0.05).

Table (2) shows comparison between the three groups regarding mean BP. There was statistical significant difference between group I and II at all period (P1 < 0.05). There was statistical significant difference between group I and III at all period (P2 < 0.05). There was no statistical significant difference between group II and III (P3 > 0.05) except period 0 and 60 min postoperatively (P3 < 0.05).

Table (3) shows distribution of VAS during static and dynamic pain among patients in the three groups postoperatively. There was statistical significant difference between the three groups regarding VAS (P1, P2 and P3 < 0.05)

Table (4) shows comparisons between the three groups regarding the total pethidine consumption. There was statistical significant difference between the three groups (P1, P2 and P3 < 0.05).

Table (1): Comparison between the three groups regarding HR (beats / min)

HR (beats / min) Intraoperative		Group I (paracetamol)	Group II (celecoxib)	Group III (pregabalin)	P1	P2	P3
Before Intubation	Range	70-106	58-107	64-105			
	Mean+SD	89.97±8.76	82.6±13.9	78.20±8.91	0.004*	0.001*	0.189
After Intubation	Range	81-116	77-99	71-105			
	Mean+SD	99.43±10.12	88.8±5.5	85.93±10.88	0.030	0.001*	0.065
(15 min)	Range	68-106	63-101	59-96			
	Mean+SD	90.17±12.87	82.6±13.2	80.80±10.00	0.014	0.001*	0.280
(30 min)	Range	67-114	61-108	58-104			
	Mean+SD	89.23±13.79	83.9±17.4	77.93±14.55	0.015	0.002*	0.078
(45 min)	Range	66-125	60-118	55-115			
	Mean+SD	101.40±18.50	87.4±18.6	88.63±16.28	0.002*	0.003*	0.390
(60 min)	Range	66-125	60-119	55-112			
	Mean+SD	97.17±16.40	88.9±17.4	82.87±17.66	0.032	0.001*	0.061
Post-Operative							
(0 min)	Range	66-115	63-108	58-100			
	Mean+SD	89.67±14.76	83.8±10.5	80.21±12.01	0.012*	0.006*	0.038*
(30 min)	Range	62-124	68-118	55-115			
	Mean+SD	93.33±20.39	87.7±11.3	83.27±17.88	0.013*	0.023	0.092
(60 min)	Range	65-125	60-99	59-114			
	Mean+SD	96.73±17.72	85.6±11.4	83.93±17.78	0.018*	0.004*	0.036
(90 min)	Range	66-112	62-109	59-105			
	Mean+SD	87.90±12.92	84.0±15.1	83.27±15.10	0.014*	0.013	0.422
(120 min)	Range	66-124	63-113	57-112			
	Mean+SD	95.10±16.31	84.8±11.2	81.87±17.45	0.006*	0.002*	0.071
After 4 hrs		71-115	69-104	61-111			
		94.63±11.87	85.50±9.23	84.45±12.57	0.001*	0.001*	0.357
(after 6 hour)	Range	68-119	61-117	57-115			
	Mean+SD	94.17±16.82	86.2±17.2	87.03±19.84	0.008	0.019	0.511

P1 comparison between group I and II, P2 comparison between group I and III, P3 comparison between group II and III

**= Significant difference with P<0.05*

Table (2): Comparison between the three groups regarding mean BP (mmHg.)

Mean BP (mmHg) Intraoperative		Group I (paracetamol)	Group II (celecoxib)	Group III (pregabalin)	P1	P2	P3
Before Intubation	Range	54-100	71-86	50-82			
	Mean+SD	85.3±10.2	78.3±4.6	69.73±9.67	0.012*	0.001*	0.023*
After Intubation	Range	70-100	72-97	61-95			
	Mean+SD	84.7±7.4	80.2±5.6	79.07±10.70	0.035*	0.012*	0.319
(15 min)	Range	70-99	71-98	60-95			
	Mean+SD	87.2±8.6	83.1±7.1	81.50±9.88	0.017*	0.101	0.096
(30 min)	Range	81-100	70-94	60-92			
	Mean+SD	88.3±5.4	81.1±7.1	73.33±8.85	0.023*	0.001*	0.039*
(45 min)	Range	70-100	72-100	61-95			
	Mean+SD	86.5±9.0	84.5±9.5	79.83±11.06	0.045*	0.01*	0.068
(60 min)	Range	70-100	70-99	62-95			
	Mean+SD	86.7±9.7	80.0±7.9	80.07±10.89	0.011*	0.015*	0.85
Post-Operative							
(0 min)	Range	75-120	78-97	65-98			
	Mean+SD	100.5±14.0	87.9±6.1	78.50±10.55	0.019*	0.001*	0.026
(30 min)	Range	77-120	75-98	66-100			
	Mean+SD	103.6±13.5	86.2±5.7	88.57±9.70	0.005*	0.001*	0.089
(60 min)	Range	74-120	76-99	65-99			
	Mean+SD	97.7±12.5	86.7±5.9	79.63±10.14	0.001*	0.001*	0.026
(90 min)	Range	74-119	78-95	66-99			
	Mean+SD	95.1±12.5	85.3±4.8	83.50±10.26	0.001*	0.001*	0.258
(120 min)	Range	65-115	75-114	66-98			
	Mean+SD	93.2±14.5	86.2±7.4	85.77±10.13	0.001*	0.002*	0.652
After 4 hrs		79-116	77-98	69-98			
		96.67±9.49	85.57±4.69	82.93±7.86	0.001*	0.002*	0.001
(after 6 hour)	Range	77-120	76-97	66-100			
	Mean+SD	100.1±13.2	85.0±5.5	80.10±9.93	0.003*	0.001*	0.068

P1 comparison between group I and II, P2 comparison between group I and III, P3 comparison between group II and III

Table (3): Distribution of VAS during static and dynamic pain among patients in the three groups postoperatively

Postoperative Pain (VAS)		Group I (paracetamol)	Group II (celecoxib)	Group III (pregabalin)	P1	P2	P3
(0 min)	Range	1-5	0-3	0-2			
	Mean+SD	2.37±1.03	1.43±1.10	1.22±0.16	0.017*	0.002*	0.013*
(30 min)	Range	1-4	1-4	0-3			
	Mean+SD	2.40±1.22	2.07±0.58	1.77±0.90	0.002*	0.002*	0.083
(60 min)	Range	1-5	0-4	0-3			
	Mean+SD	2.93±1.08	1.83±0.91	1.70±1.02	0.021*	0.001*	0.101
(90 min)	Range	1-6	0-5	0-3			
	Mean+SD	2.50±1.17	2.23±1.22	1.67±0.76	0.041*	0.001*	0.038
(120 min)	Range	1-4	1-5	0-3			
	Mean+SD	2.60±1.13	2.37±0.89	1.50±0.97	0.044*	0.003*	0.015*
After 4 hrs	Range	1-4	1-3	1-2			
	Mean+SD	2.53±1.04	1.80±0.71	1.13±0.15	0.012*	0.006*	0.015*
(after 6 hour)	Range	0-4	1-5	0-2			
	Mean+SD	2.50±1.20	2.10±0.99	1.07±0.15	0.045*	0.002*	0.015*

P1 comparison between group I and II, P2 comparison between group I and III, P3 comparison between group II and

III

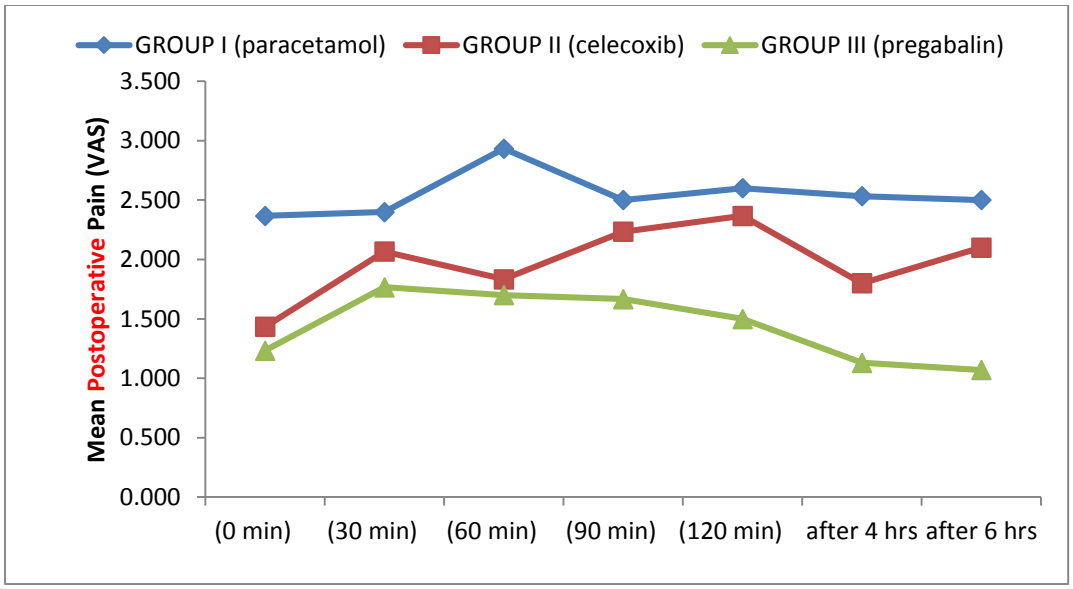

Figure (1): Distribution of VAS during static and dynamic pain among patients in the three groups postoperatively

Table (4): Comparisons between the three groups regarding the total pethidine consumption.

Pethidine consumption	Group I (paracetamol)	Group II (celecoxib)	up III (pregabalin)
Range	71-235	0-170	0-130.5
Mean	151.18	54.35	41.21
S.D.	54.00	45.83	31.25
P1	0.0001*		
P2	0.001*		
P3	0.035*		

P1 comparison between group I and II, P2 comparison between group I and III, P3 comparison between group II and III

Regarding postoperative level of sedation, there was no statistical significant difference between the three groups.

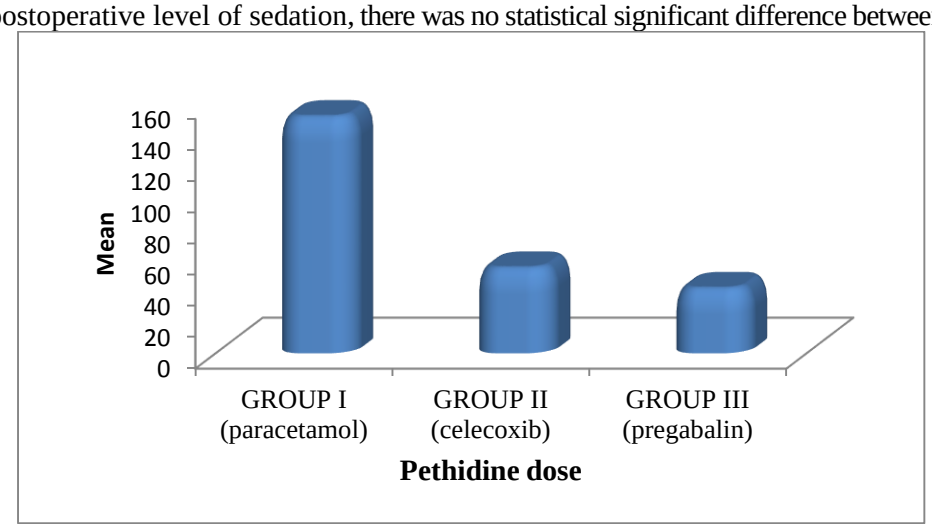

Figure (2): Comparisons between the three groups regarding the total pethidine consumption.

The postoperative blood glucose showed insignificant difference between the three groups.

Table (5) shows comparison between the three groups regarding postoperative side effects. There was no statistical significant difference between the three groups (P1, P2 and P3 > 0.05).

Table (5): Comparison between the three groups regarding postoperative side effects

Post-Operative side effects	Group I (paracetamol)		Group II (celecoxib)		Group III (pregabalin)		P1	P2	P3
	No.	%	No.	%	No.	%			
Nausea	2	6.7	0	0.0	0	0.0	-	-	-
Vomiting	1	3.3	0	0.0	0	0.0	-	-	-
Abdominal pain	0	0.0	0	0.0	0	0.0	-	-	-
Dizziness	0	0.0	**0**	0.0	**0**	0.0	-	-	-
Excessive sedation	0	0.0	0	0.0	0	0.0	-	-	-
Blurring of vision	**0**	0.0	0	0.0	0	0.0	-	-	-

DISCUSSION

Freedom from pain should be a basic human right, limited only by our knowledge to achieve it [17]. Recent advances in the pathophysiology of pain have suggested that it is possible to prevent or to attenuate the central neural hyperexcitability that contributes to enhanced postoperative pain [18]. Pain is one of the main reasons for overnight hospital stay after day case surgery [19].

In the current study, there was no statistically significant difference between the three studies regarding their demographic data (P > 0.05).These results were in agreement with **Esmat and Farag** [20]; the results of the current study did not show significant difference in the demographic data of the groups of patients as regard age and body weight. These results eliminate the effect of demographic data on the outcome results.

The heart rate in our study showed a statistically significant difference between group I and II at all periods (P1 < 0.05). There was statistically significant difference between group I and III at all periods (P2 < 0.05). There was no statistically significant difference between group II and III (P3 >0.05) except period 0 and 60 min postoperative (P3 < 0.05). Also the mean atrial blood pressure showed a statistical significant difference between group I and II at all period (P1 < 0.05). Also, there was statistical significant difference between group I and III at all period (P2 < 0.05). There was no statistical significant difference between group II and III (P3 > 0.05) except period 0 and 60 min post-operative (P3 < 0.05).

In agreement with our study, there were many studies about the hemodynamic data associated with pain postoperatively.Vital signs are important to direct pain sensitivity as, in case of pain, blood pressure, respiratory and cardiac frequencies are modified. Thus, patients' postoperative exposure to pain provokes alterations in hemodynamic data, demanding further research on the associations between pain intensity and its effects on modifications in vital signs [21].

In agreement with our study **Esmat and Farag** [20] he carried his study on similar groups as our study, hefound that there was a significant decrease in the mean heart rate in the group (II) and group (III) compared to group (I) at 30 min, 1 h, 1.5 h, and 2 h postoperatively. There was not a significant difference in the mean heart rate in the group (III) compared to group (II) at any time postoperatively and there was not a significant difference in the mean heart rate between the three groups at 6 h postoperatively[20].

Also, in the same study there was a significant decrease in the mean systolic blood pressure in the group (II) and group (III) compared to group (I) 30 min, 1 h, 1.5 h, and 2 h postoperatively. There was not any significant difference in the mean systolic blood pressure in the group III compared to group (II) at any time postoperatively and there was no statistically significant difference between these groups of patients 6 h postoperatively. Arterial O_2saturation (SPO_2%) showed insignificant difference between the three groups regarding arterial O_2 saturation (P1, P2 and P3 > 0.05) [20].

Regarding VAS during static and dynamic pain among patients in the three groups at zero time postoperatively, there was statistically significant difference between the three groups regarding VAS (P1, P2 and P3 < 0.05) it was found that celecoxib 200mg orally and pregabalin 150mg orally had the same effect on pain recovery without signficiant difference while paracetamol 1gm orally showed a very limted effect on pain recovery.

These results are in agreement with the findings of **Girija *et al.*** [22] who reported that the administration of single preoperative dose of oral pregabalin 150 or 300 mg was effective in reducing postoperative pain and total fentanyl consumption in patients undergoing lumbar laminectomy and discectomy.

Agarwal *et al.* [23] also reported that oral pregabalin 150 mg administered before the operation was effective in reducing postoperative pain and the

postoperative patient-controlled fentanyl requirement in patients undergoing laparoscopic cholecystectomy.

These results were partially consistent with **Peng *et al*.** [24] who reported that multiple doses of pregabalin resulted in superior analgesia only in the first 90 min over placebo. Pregabalin 75 mg offered better analgesia compared with pregabalin50 mg. However, pregabalin did not result in a reduction in opioid consumption, clinical meaningful side effects or an improvement in quality of recovery.

Agarwal *et al*. [23] reported that a preoperative 150 mg dose of pregabalin in patients who underwent laparoscopic cholecystectomy effectively reduced opioid consumption and decreased postoperative pain. Another study found that 100 mg of pregabalin was ineffective in enhancing recovery and relieving postoperative pain after minor gynecologic interventions. **Bahgat *et al.*** [25] investigated the effects of 150 and 300 mg doses of pregabalin as preemptive analgesics in patients who underwent laparoscopic cholecystectomy. A total of 150 mg of pregabalin was indicated to be more effective in acute pain and treating safer because side effects such as excessive sedation, headache, blurring of vision, and postoperative nausea and vomiting were not reported.

These observations are in accordance with a number of studies [26]. Our result showed that use of low concentration of pregabalin (150 mg) was significantly more effective than other groups in postoperative pain management. Two other studies revealed that low concentration of pregabalin did fail to decline postoperative pain that may be due to single low-concentration of pregabalin administrated or the heterogeneous characteristic of cases [27,28]. In this study they demonstrated that the higher concentrations of pregabalin (300 mg) improved VAS score significantly. Similar results were observed in the studies including patients with laparoscopic cholecystectomy and abdominal hysterectomy [29-30]. However, in some other studies, higher concentration of pregabalin was associated with an increased risk of adverse effects [31].

On the contrary, **Jokela *et al.*** [32] concluded that preoperative concentrations of 300 mg of pregabalin not only failed to decrease postoperative pain score after laparoscopic hysterectomy, but also was associated with an increased incidence of adverse effects (dizziness, blurred vision and headache).

Preoperative use of celecoxib previously showed to be beneficial in enhancing pain control in other areas of orthopedic surgery. In the knee arthroscopy literature, **Ekman *et al.*,** [33] showed that a dose of 400 mg of celecoxib administered 1 hour before surgery as well as a dose of 200 mg of celecoxib at the first request for pain medication postoperatively reduced the consumption of opioid medication and also reduced the incidence of opioid-related adverse events in the early postoperative period for patients undergoing knee meniscectomy. Similarly, studies of pain management after knee arthroplasty showed a benefit of celecoxib administered shortly before and after surgery for reducing pain and opioid consumptions and increasing knee range of motion[34]. Known severe side effects of celecoxib include cardiovascular thrombotic events, myocardial infarction, stroke, and severe GI upset.

Postoperative Level of sedation in our study showed insignificant difference between the three groups regarding postoperative level of sedation (P1, P2 and P3 > 0.05).

This result was supported by the study of Girija et al. who reported that the sedation score was higher postoperatively in patients received single preoperative dose of oral pregabalin 300 mg than patients received single preoperative dose of oral pregabalin 150 mg undergoing lumbar laminectomy and discectomy [22].

In this study there were no postoperative side effects in groups treated withcelecoxib and pregabalin, only 2 cases in paracetamol-treated group had nausea and one case had vomiting. There was no statistical significant difference between the three groups regarding postoperative side effects (P1, P2 and P3 > 0.05).

CONCLUSION

In conclusion, this study validates the efficacy of pre-operative administration of oral pregabalin in a dose of 150 mg 2 hour before surgery, in significantly attenuating pain intensity and total meperidine consumption during the first 6 hours postoperatively. The study further verified that the drug possessed a safe haemodynamic profile and was free from inducing respiratory depression during the intra-operative period. The study meanwhile ruled out any alteration in sedation levels, or any involvement of side effects induced by the tested dose of the drug, during the first 6 hours postoperatively.

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