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Evaluating the Effect of Preoperative Duloxetine Administration on Postoperative Pain in Patients under Abdominal Hysterectomy

H. Sattari (MD)[1], M. Noroozi (MD)*[2], M. Hashemian (MD)[1], M.R. Doroodian (MD)[1], F. Mansoori Nasab (MD)[1]

1.Department of anesthesiology and pain medicine, faculty of medicine, Kerman University of Medical Science, Kerman, I.R.Iran

2.Department of anesthesiology and pain medicine, faculty of medicine, Isfahan University of Medical Science, Isfahan, I.R.Iran

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ABSTRACT

BACKGROUND AND OBJECTIVE: Postoperative pain management is considered as a part of recovery. Duloxetine (DLX), an anti-depressant medication, is a possible choice for the multimodal anesthetic strategy. We aimed to evaluate the effect of Duloxetine on postoperative hysterectomy pain management in patients who underwent hysterectomy.

METHODS: In this randomized double-blind clinical trial, 60 patients aged 18-85 years with ASA I and II who were candidates for hysterectomy were randomly assigned to two group of 30 patients taking duloxetine (60 mg capsule) or placebo (starch). Opioid use, postoperative pain due to visual analogue score, vital signs and quality of recovery (Recovery-40 form), vital signs before induction of anesthesia, immediately after surgery, at isoflurane induction and after surgery every 15 minutes were reviewed and compared in two groups.

FINDINGS: The amount of opioids in the duloxetine group decreased insignificantly. Postoperative pain in recovery and ward in duloxetine group (2.7±0.99 and 1.8±0.66, respectively) compared to placebo group (4.86±1.51 and 4.86±1.51, respectively) decreased significantly (p= 0.006 in recovery and p= 0.001 in ward). The quality of improvement in recovery (156.22±24.25 in the duloxetine group and 125.48±16.49 in the placebo group) was in favor of the effectiveness of duloxetine (p= 0.001).

CONCLUSION: In conclusion, DLX is a beneficial drug to be used in multimodal anesthesia strategy especially in improving postoperative pain and quality of recovery in abdominal hysterectomy.

KEY WORDS: *Duloxetine Hydrochloride, Postoperative Pain, Hysterectomy, Analgesics, Opioid.*

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***Corresonding Author: M. Noroozi (MD)**

Address: Department of anesthesiology and pain medicine, faculty of medicine, Isfahan University of Medical Science, Isfahan, I.R.Iran

Tel: +98 31 33431722

E-mail: Mehrdadnoroozi48@yahoo.com

Introduction

Postoperative pain is the body's complex physiological response to tissue damage, visceral dilatation, or the disease itself, and many people consider it the most unpleasant postoperative complication (1). Post-operative pain control will result in more patient satisfaction and shorter duration of hospital stay (2). There are different methods for post-operative pain management, including administration of intravenous opioids, NSAIDs, and local anesthesia, which have their own side effects (3).

Before introducing multimodal-analgesic strategy, opioids were the main analgesic with many side effects (4). Multimodal-analgesia provides sufficient analgesia through combination of drugs in moderation in order to achieve anticipated postoperative pain control with minimal side effects. Many drugs have been introduced that effectively reduce opioids consumptions and accelerate patients' recovery, including antidepressant drugs such as Serotonin-norepinephrine reuptake inhibitors (5, 6).

It was shown that preoperative consumption of DLX drug, which is SNRIs, has promising effects on postoperative pain management, reducing opioids intake and delivering anticipated recovery (7, 8). Previous studies in gynecological operation, which induces moderate to severe post-operation pain, have shown that DLX had a successful result in analgesia (9, 10). The effect of DLX on postoperative abdominal hysterectomy pain control was studied amongst 63 patients, demonstrating an adequate decrease of opioids consumption and recovery (11). Although the role of DLX in postoperative hysterectomy pain has been partially studied, considering some inconsistencies on this drug's exact role, we aimed to evaluate its effect on postoperative hysterectomy pain management, vital signs and quality of recovery.

Methods

This double-blinded, randomized clinical trial was conducted at Afzalipour Hospital, Anesthesiology department, and was registered in the Iranian registry of clinical trials (IRCT20120922010900N5) and was approved by the local Ethics Committee of Kerman University of Medical Sciences with the code number of IR.kmu.REC.1396.1917. Inclusion criteria were candidates with an age range of 18-85 and American society of Anesthesia (ASA) physical status I (without systemic disease) and II (with controlled systemic disease) with abdominal hysterectomy due to endometriosis, ovarian or cervix cancer, fibroid, and abnormal vaginal bleeding when all other treatments have been tried and failed. Those who were on narcotics, painkillers, steroids, those younger than 18 or older than 85 years old, those with heart failure, liver failure or renal failure, those with uncontrolled hypertension or endocrine disorders, those with body mass index more than 40, heart rate less than 50, prolong PR interval (>0.2 milli second) or any heart block based on their electrocardiograph and finally those who were known case of convulsion or bipolar disorder were excluded.

The sample size according to previous study with alpha 5% and power 90% was determined 26 patients in each group (12). In order to improve the results and increase the statistical power of the samples in each group, we increased the sample size to 30 individuals in each group. The patients were randomly allocated in either the case group or the placebo group based on a computer-generated chart. In the preoperative examination, the patients were informed of the method and goals of the investigation and each eligible patient was approached to obtain written consent. In this study, the person administering anesthesia did not know the prescription medication method and the person who checked the severity of pain and vital symptoms. In order to equalize recovery time, patients were allowed to stay in the recovery room for 45 minutes.

Anesthetic drugs were exactly the same in each group except for DLX. Prior to anesthesia, vital signs such as heart rates/minute, non-invasive arterial oxygen saturation (SaO_2) and blood pressure were documented. Two hours before inducing anesthesia, 60 milligram DLX (commercial name: Loxeta, in the form of capsule, Obeidi company) was given to patients in intervention group and placebo made with starch to the control group. General Anesthesia was achieved by 0.05 mg/kg Midazolam and 3 mcg/kg Fentanyl, 0.5 mg/kg Atracurium and 2 mg/kg Propfol intravenously. MAC of Isoflurane was used for anesthesia maintenance. If heart rate and mean atrial pressure increased more than 20% from the baseline, 50 mcg fentanyl was given. After operation, pain scores according to visual analogue score (VAS) were evaluated and recorded during at least 45 minutes stay at recovery every 15 minutes and also 2, 4, and 24 hours after operation by a blinded technician. If VAS was described more than 4, 25 mg IV pethidine was given to the patient. Every 6 hours, 1 g IV acetaminophen was also ordered. As secondary outcomes, twenty-four hours after surgery, Quality of Recovery-40 (QOR-40) scores forms were

filled via patients (13). We asked the patients to report any symptoms as adverse effects of DLX. Vital signs were checked before anesthesia induction, immediately after starting surgery, in the time of isoflurane induction, and after surgery until the end of recovery every 15 minutes.

We analyzed the data using SPSS software (version 17; IBM, Armonk, USA). Normality of data distribution was checked by Kolmogorove-Smirnov test. For comparing the characteristics between groups at the baseline, independent samples t test (or x2 for qualitative variables) was used. To assess changes within groups, paired t-test and Wilcoxon signed-rank test were used for the data with normal distribution and for skewed data, respectively. Differences between groups were evaluated by One-way ANOVA test. In the case of abnormal distribution, we used Kruskale-Wallis test. Repeated-Measure-Anova was used for evaluating the effect time. $p<0.05$ was considered statistically significant.

Results

Sixty candidates for abdominal hysterectomy from March to June 2017 and age range of 23 to 78 were eligible for current study. Measured SaO_2 did not change over time and was not significantly different among groups (Figure 1). Heart rate and blood pressure before surgery, every 15 minutes during surgery, at the end of the surgery, at recovery and at discharge from recovery were not significantly different between the two groups. (Figure 2 and Figure 3 respectively). Pain scores were significantly different between the two groups. Those who took DLX experienced significantly less pain (2.7±0.99) in comparison with those who did not (4.86±1.51) in the recovery unit (p=0.006). Pain score in the ward was also significantly lower in DLX group (1.8±0.66) compare to the placebo group (4.97±1.92), (p=0.001), (Table 2). Significant difference was observed in QOR-40 between groups. Mean score of DLX group was 156.22 and 125.48 for placebo group with p=0.001. (Table 3). Regarding opioid use, people who took duloxetine before surgery needed more opioid compared to the placebo group, although it was not statistically significant (5.37±2.41 vs. 6.03±2.42 mg) (Table 3).The most frequently reported side effect was nausea (18%), which was released after IV anti-emetics. However, no significant difference was seen between the two groups in terms of side effects.

Table 1. Demographic and baseline characteristics of both groups

Group Indicator	Placebo (Mean±SD)	Duloxetine (Mean±SD)	P-value
Age(y)	59.10±6.28	59.18±9.10	0.96
Weight(kg)	61.40±8.65	64.87±8.34	0.083
Duration of anesthesia (minutes)	102.13±31.16	90.51±23.18	0.054
ASA physical status I (N)	14	10	>0.05
ASA physical status II (N)	20	16	>0.05

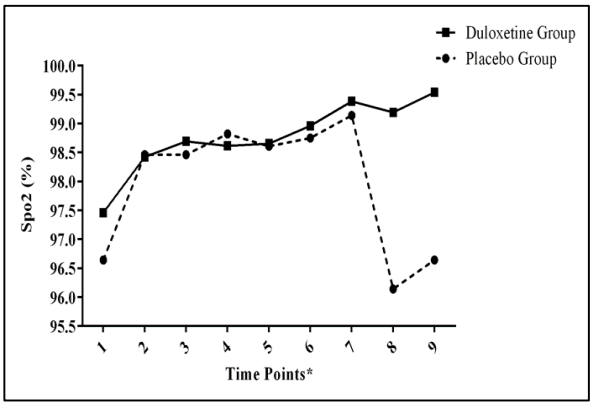

Figure 1. Comparison of mean systolic blood pressure through surgery and post-operative between placebo and DLX group. *Time points: 1: pre-operation, 2: First 15 min of surgery, 3:Second 15 min of surgery, 4: Third 15 min of surgery, 5: Fourth 15 min of surgery, 6: End of surgery, 7: In recovery, 8: At discharge from recovery.

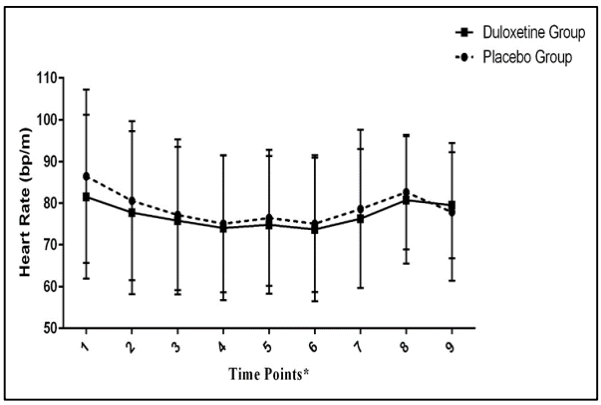

Figure 2. Comparison of mean heart rate through surgery and post-operative between placebo and DLX group. *Time points: 1: pre-operation, 2: First 15 min of surgery, 3: Second 15 min of surgery, 4: Third 15 min of surgery, 5: Fourth 15 min of surgery, 6: End of surgery, 7: In recovery, 8: At discharge from recovery.

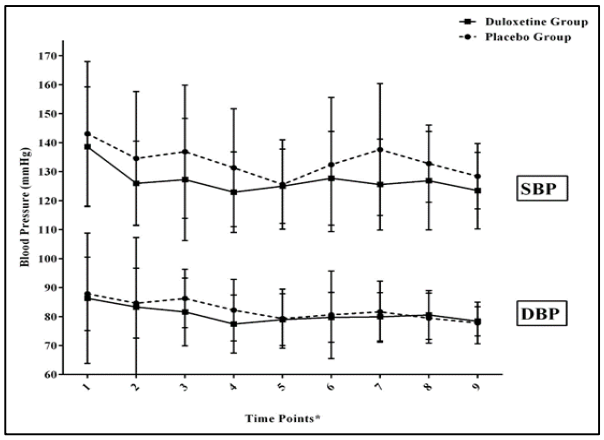

Figure 3. Comparison of mean SaO_2 through surgery and post-operative between placebo and DLX group. ***Time points: 1: pre-operation, 2: First 15 min of surgery, 3: Second 15 min of surgery, 4: Third 15 min of surgery, 5: Fourth 15 min of surgery, 6: End of surgery, 7: In recovery, 8: At discharge from recovery.**

Table 2. Comparison of pain scores in placebo and DLX groups in recovery and ward unit

	Placebo group (Mean±SD)	DLX group (Mean±SD)	P-value
Recovery	4.86±1.51	2.7±0.99	0.006
Ward	4.97±1.92	1.8±0.66	0.001

Table 3. Comparison of QOR-40 scores and opioids consumption between placebo and DLX group

	Placebo group Mean±SD	DLX group Mean±SD	P-value
QOR-40 score	125.48±16.49	156.22±24.25	0.001
Opioid consumption in recovery unit (mg)	5.37±2.41	6.03±2.42	0.379

Discussion

Perioperative consumption of 60 mg DLX significantly reduced postoperative pain and increased quality of recovery. Although patients who took DLX had significantly less pain than those who did not, opioid consumption was still much alike. As for evaluated standard monitoring, no significant difference was observed between groups. Multimodal analgesia has been used by Kim et al. in managing postoperative pain and it appeared to be successful in managing pain, reducing opioids intake and enhancing recovery (14). Many trials have introduced antidepressants as successful adjutant drugs for multimodal analgesia, which had shown positive results in managing postoperative pain and recovery (9, 15). Onutu reviewed DLX, a second line antidepressant as adjuvant drug for analgesia and suggested it as a promising choice, which was in line with other studies (7, 16, 17). The mechanism supposedly works through inhibiting reuptake of spinal noradrenalin and serotonin leading to pain inhibition by SNRIs (18).

Short-term administration of DLX raises extracellular monoamine levels, thereby inducing analgesic effects from spinal tract ways (19). It is shown that DLX reduces postoperative pain by increasing spinal norepinephrine and serotonin levels as well as activating alpha 2 noradrenergic or 5-HT2A receptors in mice (20). Recently, the inhibitors of norepinephrine and serotonin absorption have been introduced into the field of analgesic drugs. They have regulatory effects on pain pathways that interfere with chronic postoperative pain (21). The study found that the enantiomer of LY227942 molecule acts similar to fluoxetine and twice as much as the negative enantiomer inhibits serotonin reuptake. it was later named DLX and its first data were published in 1988 (22). The bonding capacity of DLX with serotonin and norepinephrine transporter is 100 times higher than other drugs in this group (23).

As we evaluated opioids consumption after 60 mg dose of DLX prior to abdominal hysterectomy, no significant difference was seen in comparison with placebo group. Castro-Alves et al. proved otherwise with similar amount of cases like ours in the same surgery. They also concluded that perioperative DLX would improve quality of recovery, which is in line with our results (11). Heyer et al. (24) also observed decreased postoperative pain and improved quality of recovery with DLX same as ours.

As for vital signs, we did not notice any difference between the two groups and there are no other studies in this regard that we know of to compare with, but few years back, Haelst et al. showed a correlation between use of SNRIs and briefer episodes of intraoperative hypotension (25). We evaluated the side effects and tolerance of DLX, indicating no impact on our patients, which was contrary to other studies (26). Abdominal hysterectomy is known as one of the most common surgeries with reported moderate to severe postoperative pain complaint (27). Our study was dedicated to evaluate this less studied issue. We showed that this drug can reduce post-operative pain and quality of recovery and slightly decrease opioids intake. Another strength of our study was its design, which was double-blinded, leading to the most accurate results. Our study faced some limitations. It was a single-center

study and sample size could be greater to be more generalizable. DLX appeared to be effective as an adjuvant drug for multimodal analgesia as it significantly reduced postoperative pain. It also improved quality of recovery in comparison with placebo group, which counts as an important quality. We could not figure a correlation between vital signs and DLX. Thus, much larger multi-center trials are recommended that consider multiple doses with follow-ups.

Conflict of interest: The authors declare that they have no conflict of interest.

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