Effect of Perioperative Duloxetine on Postoperative pain relief following Anterior Cervical Microdiscectomy and fusion. A Pilot Study

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INTRODUCTION

Pain can be classified into nociceptive pain (which is due to injury to body tissues as in post-traumatic joint pain), neuropathic pain (due to damage and/or dysfunction of peripheral nervous system as in diabetic peripheral neuropathy and/or central nervous system (brain and spinal cord) as in spinal cord injury) (37) and mixed pain (i.e.: a mixture of both peripheral and central neuropathic pain as in cervical radiculopathy, low back pain).

Over time, and when neuropathic pain is long standing—which is so often the case—permanent neurologic changes, i.e. neuroplasticity may occur that perpetuate the pain (16). Consequently, both peripheral and central sensitization take place, making neuropathic pain more difficult to treat and that is how it ends up frequently with chronic pain disorders. There is an intimate relation between long standing pain (especially neuropathic) and development of depression and sleep disturbance that lead again to exaggerated pain perception and thus the production of a vicious circle.

During spinal decompression, there is nociceptive pain due to surgical tissue injury to both soft tissues and bony structures, in addition to neuropathic pain resulting from manipulation of neurological tissue in order to decompress them.
Duloxetine hydrochloride is one of a newer types of antidepressant drug, which is a potent, selective and relatively balanced (34) serotonin and noradrenaline reuptake inhibitor (SNRI) (11, 40), with weak effects on dopamine reuptake. It has no significant activity for muscarinic, cholinergic, alpha2-adrenergic receptors, H1-histaminergic, opioid, glutamate, and gamma amino butyric acid (GABA) receptors in vitro and it does not possess monoamine oxidase (MAO) inhibitory activity(4).

It possesses an analgesic effect (28), and this is believed to be related to the serotonin and norepinephrine modulating effect on descending inhibitory pain pathways in the brain and spinal cord (5,8,32). Some have argued that it may relieve the depression and anxiety experienced by patients in pain (2,14,17). It might also block N-methyl-D-aspartate (NMDA) receptors or sodium channels or enhance the body's own endorphin system; therefore it has been shown to be effective in treatment of painful neuropathy or chronic pain (1,15) and it may have a role in reducing postoperative pain, especially when combined with opioid therapy (19).

It has been reported to produce modest analgesic efficacy in neuropathic and inflammatory pain models in animals (20, 33). However, the effects of simultaneously inhibiting both serotonergic and noradrenergic reuptake in models of acute nociception as well as persistent hyperalgesia and allodynia are not well studied.

To our knowledge, there is no other study in literature which used duloxetine or studied it for postoperative pain relief following Anterior Cervical Microdiscectomy and Fusion (ACDF) which made this study a pilot study. Therefore our primary aim was to investigate the analgesic efficacy of duloxetine through detecting the effect of duloxetine on narcotic and analgesic requirements both intra and postoperatively in patients undergoing one level (ACDF), the secondary objective was to assess timing for first rescue analgesia, ambulation time, pain score using VAS, patient satisfaction as well as the adverse effects of the studied drug.

MATERIALS AND METHODS

After obtaining our university hospital ethical committee approval, an informed written consent was signed by 44 patients of both sexes, aged between 38-65 years, ASA I and II and were scheduled for one level (ACDF) after failure of conservative management.

Inclusion criteria included patients with single level cervical disc prolapsed and or osteophyte complex causing radiculopathy who were on duloxetine for a minimum of two weeks as a part of their conservative management and their radiculopathy proved intractable so they are indicated for surgical decompression.

Exclusion criteria were: patients with myelopathy, MRI showing cord malacia, history of allergic reaction to any of the study drugs, history of opioid addiction, use of drugs known to interact with study agents, history of drug or alcohol abuse, and abnormal renal and liver function tests. Patients with previous cervical surgeries or had chronic pain syndrome, psychiatric disorders, those receiving opioid analgesic medications in the last 24 hours preoperatively were excluded too.

This study is designed to be a prospective, double blind (for the patients and the assessor), controlled study. It was run between May 2011 and October 2012 at three orthopedics spine surgery units in Cairo including those of our university hospitals by the same orthopedic spine surgeon author with the same technique. Single level (ACDF) using standard anterior approach, left sided always, using PEEK cage filled with self-bone taken from the operative site, mostly osteophytes, mixed with artificial bone extender for interbody fusion after discectomy, foraminotomy and preparation of the endplates of the adjacent vertebrae. All cases were subjected to one level ACDF.

Patients were divided into two equal groups (22 each): Duloxetine Group (D): in which patients were given a capsule of 60 mg duloxetine hydrochloride (Cymbalta, Eli Lilly& Company, Ind. USA) daily for at least two weeks before the surgery as a part of their conservative management and continued 2 weeks post operatively; Control Group (C): includes patients who were not having duloxetine as part of their preoperative conservative management or had it for a short period of less than one week and thus it was not yet functionally affecting the patient. They were given an oral capsule of placebo (starch containing capsule that looks exactly as the duloxetine capsule) once daily for 2 weeks postoperatively.

During the preoperative visit, history and investigations were checked (ECG, complete blood count, liver and kidney functions tests) and all patients were made familiar on how to use the visual analogue scale (VAS) where 0 being ‘no pain’ and ‘10’ being the maximal worst pain.
Before induction, all patients were preloaded with 500 ml ringer lactate; and a baseline mean arterial blood pressure, heart rate and oxygen saturation were recorded. General anesthesia was induced by 1 ug/kg fentanyl IV, 2mg/kg propofol IV, and endotracheal intubation was performed after IV administration of atracurium besylate (tracrium) (0.5 mg/kg). Anesthesia was maintained through inhalation of a mixture of oxygen (3 L/min) 0.5 – 1.5% isoflurane and atracurium (0.05 mg/Kg) as intermittent dose as required to ensure proper muscle relaxation.

Hemodynamics as mean arterial blood pressure (MABP), heart rate (HR), and oxygen saturation (SPO2) were recorded every 10 minutes till the end of the operation. End tidal concentration of isoflurane was assessed every 20 minutes till the end of the operation too.

Dose adjustment of isoflurane concentration and additional intraoperative fentanyl consumption were based on clinical signs and hemodynamic measurements as signs of inadequate analgesia were defined as increase in HR and MABP>20% from base line. This was treated by 1ug /kg of fentanyl as top-up doses and increasing isoflurane concentration in case of inadequate response to fentanyl. Total amount of intra operative fentanyl consumption and isoflurane concentration consumption were also recorded. If there was a decrease in MABP>20% from base line, the patient received a 500 ml saline infusion, and if no response 5 mg ephedrine would be given. If HR decreased to 45beats/ minute, atropine 0.5mg was given. At the end of the surgery, residual muscle paralysis was antagonized by a mixture of 0.01 mg/kg atropine and 0.05 mg/kg neostigmine. A single observer who was blinded to the groups took all the measurements.

Recovery time was recorded (time from stoppage of anesthesia till the patient reaches modified Aldrete score of 9-10) and patients were transferred to post anesthesia care unit (PACU). A hard cervical collar was applied to all patients after surgery and for at least 2 weeks post-surgery and was taken of gradually according to follow up x rays showing the evolving interbody fusion of the adjacent vertebrae.

A standard analgesic regimen of 1gm IV paracetamol (perflagan, Bristol-Myers Squibb Pharmaceutical Limited NY,USA) every 6 hours was given during the first 24hours to each patient, in addition to 50 mg pethidine IM given (with a maximum of 50mg pethidine dose /8 hrs), when the VAS was perceived by the patient to be 4 or more. No routine analgesic was given in the second 24 hours, unless their VAS was ≥4, so that the patient would be given IV one gram of paracetamol (Perfalgan), with a maximum dose of one gm every 6 hours.

The nursing staff, who were blinded to the patient’s group assignment, assessed time to first rescue analgesic (the time interval between full recovery and the time at which VAS was perceived by the patient to be 4 or more) and the post-operative pain using VAS starting from 0 time (patient’s full recovery in PACU) and then at 2, 4, 6, 12, 24, 36 and 48 hours postoperatively. Total doses of pethidine consumption over the 1st 24 hours and number of patients who needed rescue pethidine were recorded too. Total amount and number of patients who needed paracetamol (1gm IV) during the second 24 hours were recorded as well.

Postoperative side effects (nausea, vomiting, insomnia, dizziness, headache, somnolence, dry mouth and pruritus) were recorded and treated. Nausea was treated by 10 mg metoclopramide I.V, Vomiting was treated by 4 mg Ondansatron I.V, Itching was treated by pheniramine maleate (45.5 mg/2 ml). Patients were asked to assess their rate of satisfaction from pain relief on four-point scale after 48 hours of surgery as: Excellent, Good, Fair, Poor. Timing of first mobilization of each group was recorded as well.

At the third day postoperatively, patients were discharged to home and were prescribed to take acetaminophen 1 g orally /6 hours, centrally acting muscle relaxant 2mg sirdalud orally/12 hours (Tizanidine, Novartis, Switzerland), Vitamin B 12 tablets twice daily, duloxetine 60 mg once daily for group (D), and placebo once daily for group (C) for the next 5 days. Patients were instructed to note the amount of pain they had at home and their analgesic needs of 1gm oral Paracetamol in case of VAS is ≥4. Broad spectrum antibiotic was given for the same period.

On the 9th day of the operation, patients visited the outpatient clinic, where the surgical stitches were removed and the patients were asked by the orthopedic residents about the total amount of rescue paracetamol needed and residual radiculopathy. Duloxetine and placebo capsules were stopped at 2 weeks postoperative. No analgesics nor muscle relaxant were needed for any patient in both groups in the second postoperative week.

Statistical analysis

Statistical analysis of data was carried out using IBM SPSS version 18 (New York, USA). A sample size of 22
patients per group was required to have a power of 80% with an level of 0.05. Data were expressed as mean± SD, percentages (%), numbers (n) and median (range). 2 or Fisher's exact test was used for categorical data. P-value less than 0.05 were considered statistically significant.

**RESULTS**

The demographic data showed no statistical significant differences in the patient’s characteristics as regards, age, sex, ASA, weight and duration of surgery (Table 1).

The intraoperative HR, MABP and SpO2 showed a non-significant difference between the two groups. Isoflurane consumption showed a non-significantly higher percentage in the control group (1.3±0.2%) than that in the duloxetine group (1.25±0.1%) (p>0.05)(Table 2).

Total amount of intraoperative fentanyl consumption was significantly higher in the control group (200.4±8.7ug) than the duloxetine group (90±5.00ug) (p<0.001). Recovery time was significantly longer in the control group (20.3±3.9) (p<0.001) as well (Table 2).

As regard time to 1st rescue analgesia was significantly longer in duloxetine group (165.3±23.1min) when compared to control group (42.11±10.1min)(p<0.001) (Table 3).

Total pethidine consumption and number of patients requesting pethidine during the first 24 hour were statistically higher in the control group when compared to duloxetine group. Timing of ambulation was significantly shorter in

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**Table 1: Demographic data, duration of surgery**

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=22)</th>
<th>Group D (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50±12</td>
<td>50±10</td>
<td>1.000</td>
</tr>
<tr>
<td>Sex (M: F) (n) (%)</td>
<td>9(40.90%):13(59.09%)</td>
<td>10(45.45%):12(54.54%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.8±6.3</td>
<td>65.4±7.7</td>
<td>0.778</td>
</tr>
<tr>
<td>ASA physical status I/II</td>
<td>11/ 11</td>
<td>13 / 9</td>
<td>0.762</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>77.9±17.2</td>
<td>70.54±20.44</td>
<td>0.206</td>
</tr>
</tbody>
</table>

*Data are expressed as mean± SD, and numbers (%) m/f: male/female.
ASA: American Society of Anesthesiologists.
C: Control D: Duloxetine.
P >0.05 was considered statistically non-significant between the two groups.

**Table 2: Total amount of intraoperative fentanyl consumption, End tidal isoflurane % and Recovery time**

<table>
<thead>
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<th>Group C (n=22)</th>
<th>Group D (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intraoperative fentanyl consumption (ug)</td>
<td>200.4±8.7</td>
<td>90±5.00</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>End tidal isoflurane (%)</td>
<td>1.3±0.2</td>
<td>1.25±0.1</td>
<td>0.301</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>20.3±3.9</td>
<td>15.7±1.35</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*Data are expressed as mean± SD.
C: Control D: Duloxetine.*
*: statistically significant difference between group C and group D.
P >0.05 was considered statistically non-significant between the two groups.
P< 0.001 was considered statistically highly significant between the two groups.
the duloxetine group (10(8-18) hr) than the control group (20(16-24) hr)(p<0.001) (Table 3).

Number of patients recorded residual radiculopathy was non-significantly less in the duloxetine group than the control group (P>0.05) (Table 3).

Patient satisfaction score showed a non-significant higher number of patients with excellent satisfaction in the duloxetine group than the control group (P>0.05) (Table 4).

There were no significant differences in the incidence of nausea and vomiting, dry mouth, headache, and pruritus between the two groups (p>0.05).

However somnolence and dizziness were significantly less in the duloxetine group in comparison to the control group (P < 0.05).

As regard the insomnia the duloxetine group (27.2%) showed a statistical higher incidence than the control group (0%) (P<0.05) (Table 5).

As regard VAS, it was statistically non-significantly less in the duloxetine group than the control all through the first 48 hours postoperatively and after one week from third day of discharge from the hospital (P>0.05) (Fig.1).

Table 3: Analgesic requirements during hospital stay and at home, timing of ambulation and Residual radiculopathy after one week

<table>
<thead>
<tr>
<th></th>
<th>Group C (n=22)</th>
<th>Group D (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to 1st rescue analgesia (min)</strong></td>
<td>42.11±10.1</td>
<td>165.3± 23.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Pethidine consumed in the 1st 24 hours (mg)</strong></td>
<td>116.4 ±22.8</td>
<td>50± 0.00</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Number of patients received pethidine(n) (%)</strong></td>
<td>22(100%)</td>
<td>16(72.72%)</td>
<td>0.028*</td>
</tr>
<tr>
<td><strong>Paracetamol consumed in the 2nd 24 hours (mg)</strong></td>
<td>1795.5 ± 251.6</td>
<td>1000±0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Number of patients received paracetamol (n)(%)</strong></td>
<td>22(100%)</td>
<td>10(45.45%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Total Paracetamol consumption at home (mg)</strong></td>
<td>5409±503.2</td>
<td>0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Number of patients received paracetamol at home (n) (%)</strong></td>
<td>22(100%)</td>
<td>0(0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Timing to ambulate the patient (hr)</strong></td>
<td>20(16-24)</td>
<td>10(8-18)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td><strong>Number of patients with residual radiculopathy (n) (%)</strong></td>
<td>3(13.63%)</td>
<td>1(4.54%)</td>
<td>0.600</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD, numbers (%) and median (range).

C: Control D: Duloxetine.

*: statistically significant difference between group C and group D.
P<0.001 was considered statistically highly significant between the two groups.
P >0.05 was considered statistically non-significant between the two groups.

Table 4: Patient satisfaction score

<table>
<thead>
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<th>Group C (n=22)</th>
<th>Group D (n=22)</th>
<th>Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excellent</strong></td>
<td>4 18.18</td>
<td>11 50.00</td>
<td>7.33 0.06</td>
</tr>
<tr>
<td><strong>Good</strong></td>
<td>9 40.91</td>
<td>8 36.36</td>
<td></td>
</tr>
<tr>
<td><strong>Fair</strong></td>
<td>6 27.27</td>
<td>3 13.64</td>
<td></td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>3 13.64</td>
<td>0 0.00</td>
<td></td>
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Because of the multiplicity of the mechanisms involved in post-operative pain, multimodal analgesic regimens with a combination of opioids and non-opioid drugs as non-steroidal anti-inflammatory drugs, ketamine, gabapentinoids (which has both antiallodynic and antihyperalgesic effects) (9), and clonidine were given to target various sites in the central and peripheral nervous system to manage postoperative pain and reduce opioid requirements and side-effects (3, 10).

A special problem occurs when the operation aims at bone healing or spinal fusion, as when this is the aim there is real need to avoid using NSAIDS. Many studies have especially reported on the effect of NSAIDs on spinal fusion, as it is increases the rate of pseudoarthrosis (13,31).

Surgical tissue injury results in both peripheral nociceptive as well as central sensitization of the dorsal horn of the spinal cord (7,41). Such neuroplastic changes can lead to hyperalgesia or allodynia in patients after surgery (39).

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the inhibition of reuptake of serotonin and norepinephrine or just norepinephrine within the central nervous system; however, other possible mechanisms of action include -adrenergic blockade, sodium channel effects, and NMDA receptor antagonism. Nevertheless, the side effect profile of the TCAs, including sedation, hypotension, anticholinergic, and cardiovascular liabilities, has limited their use in the treatment and management of neuropathic and other persistent pain states. Thus, the more selective dual uptake inhibitors may offer a safer alternative.

Our study showed that the intake of 60 mg duloxetine 2 weeks preoperative at least and postoperative in ACDF resulted in less consumption of intraoperative fentanyl, decrease in both total number of patients and total amount of postoperative narcotics in the first 24 hours, also it decreases the total number of patients and total amount of postoperative analgesic for the second 24 hours and one week after discharge from the hospital, this in addition to prolonged time of first rescue of analgesia and early ambulation time. Pain scores were statistically non-significant between the two groups all through the duration of the study and there was no significant difference in the residual radiculopathy after one week from the surgery between duloxetine and control group.

Duloxetine is a potent antidepressant drug whose analgesic mechanism is unknown. Some have argued it works by relieving the depression and anxiety experienced by patients in pain. It has also been proposed that it might activate the “descending” pathways from the brain, helping to dampen “ascending” pain signals from the body. In addition, It might block the NMDA receptors or sodium channels or enhance the body's own endorphin system. Theoretically these actions should make it a good pain modulating agent (4,5). Serotonin modulates both pro-nociceptive and anti-nociceptive descending effects on central pain pathways from the brainstem. Noradrenaline has a predominantly anti-nociceptive effect. Balance between facilitation and depression of pain pathways is important for normal function. Drugs that inhibit the reuptake of serotonin and noradrenaline potentiate monoamine neurotransmission in the descending inhibitory spinal pathways and so reduce nociceptive afferent transmission in the ascending spinal pain pathways. Potentiation of both serotonin and noradrenaline is required to produce effective analgesia. The action of drugs such as duloxetine is independent of their effects on depression (28). Onset of benefit occurs within days, earlier and at lower doses than in depression. Furthermore, they have similar effects on pain in depressed and non-depressed people (12).

Many studies support the efficacy of duloxetine 60 mg as there was moderately strong evidence that this dose reduce pain in both painful diabetic peripheral neuropathy (DPNP) and fibromyalgia (22). As dose of 20 mg or 40 mg (<60 mg) was not effective in the management of DPNP, and there is no evidence that 120 mg/day confers a significant additional benefit over 60 mg/day (6).

Our inclusion criteria included recruiting only those patients who had duloxetine long enough preoperatively as a part of their conservative management regimen and then proved to be surgically indicated, so that we can be sure that the drug is really fully functional in the post-operative period. That period was at least two weeks before the operation as the onset of action usually takes 1-4 weeks and even the antidepressant and mood elevation action that might be one of the reasons this drug helps pain suffering individuals, needs at least one week to commence.

For ethical considerations we did not allow patients to suffer pain (VAS ≥4). Any patient that suffered worse pain was offered rescue analgesia, in the form of pethidine in the first 24 hours and in the form of IV paracetamol in the second 24 hours. Thus we expected that both groups shall show similar VAS scores and show no statistically significant difference between the two groups in this aspect. Our assumption proved true as shown in Fig (1) Table (3).

Our assumption was again right. Our study showed a significant longer time to first rescue analgesic in the duloxetine group than the control one, we think that this maybe due to the synergistic effect of duloxetine and the intraoperative fentanyl.

Our assumption was again right. Our study showed a significant longer time to first rescue analgesic in the duloxetine group than the control one, we think that this maybe due to the synergistic effect of duloxetine and the intraoperative fentanyl.

In addition, the analgesic requirement of pethidine during the first 24 hours postoperatively was significantly lower in the duloxetine group. This may be explained by the more potentiation of the action of pethidine in the duloxetine group so this leads to less need of narcotics as selective norepinephrine reuptake inhibitors may
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significantly increase the intensity and duration of pethidine antinociceptive activity via both \(\alpha\)-adrenergic and opioid receptors as morphine do. This goes as well with a recent animal study also demonstrated that the norepinephrine reuptake inhibitor maprotiline increased morphine antinociceptive activity when administered intrathecally) 29). Another study done by Siddique et al. (35) showed that a combination of morphine and duloxetine produced a significant increase in reaction time both in tail-flick method suggesting additive antinociceptive action. Therefore that combination therapy would theoretically minimize the dose requirements and thus the potential adverse effects.

Those studies support our assumption that was later proved by our results that duloxetine might be an effective modulator of postoperative pain, especially when combined with opioid therapy.

This is a very significant result that means that having duloxetine in a fully functional for the perioperative period shall decrease pethidine requirement and thus decreasing pethidine side effects which was proved right in our study by lower rate of postoperative complications in the duloxetine group than the control group. There was less dizziness, one of the most important causes of delayed patient ambulation. That was –in our opinion –the main reason why we got a statistically significant difference between the two groups as regards time of first ambulation as in Table (3). Faster ambulation is a source of relief for both patients and treating medical team.

The paracetamol requirement during the second 24 hours was significantly higher in the control group than the duloxetine group, this may be suggested due increases norepinephrine reuptake and probably activates \(\alpha\)-adrenoceptors to mediate its antinociceptive effect (28). In addition, the paracetamol requirement at home were significantly higher in the control group than the duloxetine group for the same explanation.

Our study showed that three patient in the duloxetine group had nausea and vomiting, nausea is having high rate among duloxetine taking patients during drug initiation, gets far better in 1-2 weeks (6), so due to the fact that our duloxetine patients were on the drug for at least 2 weeks preoperative, we did not see more patients still suffering from nausea. However, the control group had six patients who suffered nausea and vomiting, this may be a side effect of repeated doses of pethidine due to higher pethidine consumption in this group. This could be another reason (less nausea) for faster ambulation in duloxetine group giving another advantage of using the drug in the perioperative period.

We had 2 patients who suffered insomnia in duloxetine group versus zero in the control group. Also 2 patients with dry mouth versus zero in the control group.

Our results coincide with Ho et al. (19) who found that perioperative administration of 60mg duloxetine (2 h before surgery and on first postoperative day) reduced postoperative morphine requirements during the first 48 h after knee replacement surgery, without significant adverse effects. Morphine requirements during the 48 h after surgery were significantly lower in the duloxetine group (19.5 mg±14.5 mg) compared with the placebo group (30.3 mg ±18.1 mg) (\(P=0.017\)). There were no statistically significant differences between the groups in pain scores (at rest and on movement) or in adverse effects.

We have one criticism against these results-although they support our theory- that in this study duloxetine was commenced immediately before surgery, all information in literature prove that the drug needs 1-2 weeks for commencement of action and thus giving it immediately before surgery does not meet the criteria for a fully functional drug.

Another study found that most people taking duloxetine will have at least one side effect. These are mostly minor and are commonly nausea, headache, feeling sick, being too awake or too sleepy, developing a headache, having a dry mouth or becoming constipated or dizzy, constipation, fatigue, diarrhea, and hyperhidrosis, in addition, the control group had a higher non-significant incidence of pruritus which may be due to high consumption of narcotics in the control group (12).

**CONCLUSION**

The current study concluded that perioperative intake of 60 mg duloxetine for two weeks in Anterior Cervical Microdiscectomy and Fusion (ACDF) resulted in less consumption of intraoperative and 48-hour postoperative analgesia with prolonged time of first rescue of analgesia, also there was significantly less need of rescue analgesia in the first postoperative week, more rapid ambulation and significantly less dizziness and somnolence in the postoperative period. There were higher rates of insomnia that did not affect patient satisfaction.
As our recommendation, we do recommend to put all patients going to elective spinal decompression and can wait for two weeks on duloxetine, 60 mg per day to get those gains.

REFERENCES


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42. Yaksh TL and Wilson PR. Spinal serotonin terminal system mediates antinociception. J PharmacolExp Ther, 1979; 208: 446-453

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