Original Research Article

A Comparative Study To Evaluate The Efficacy of Duloxetine In Different Doses For Postoperative Pain Relief In Patients Undergoing Lumbar Spine Surgery - A Randomised Double Blind Controlled Study

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Abstract

Introduction: For an early postoperative recovery it is essential to achieve adequate postoperative pain management. So the primary aim of postoperative pain management is to provide adequate pain relief with minimum medication and reduce the risk of Chronic Post Surgical Pain (CPSP). In spinal decompression surgery surgical tissue injury to soft tissues and bony structures results in nociceptive pain, in addition to neuropathic pain resulting from manipulation of neurological tissue. Duloxetine (SSNRI) was introduced in the field of pain management as an adjuvant, pertaining to its antinociceptive effect and ability to modulate pain pathways as it could interfere with chronic post surgical pain occurrence. Duloxetine may play an uncharacterized role in reducing acute postoperative pain as well as reducing dose of analgesic consumption. **Materials and Methods**: 120 patients of ASA grade 1 and 2 were randomized into 3 groups as Group I (placebo, n=40), Group II (Duloxetine 40 mg, n=40), Group III (Duloxetine 60 mg, n=40). The patients received placebo or the study drug 1 hr before and 24 hr after surgery. DemoFigic data, vital signs, postoperative pain scores (NRS) and any side effects were recorded. **Results**: Time for first rescue analgesia was significantly longer in group III as compared to group I and II. Duloxetine 60 mg provided equivocal analgesia (similar NRS score) as compared to Duloxetine 40 mg and placebo. **Conclusion:** Our data suggest that time for first rescue analgesia was longer in Duloxetine 60 mg in comparison to Duloxetine 40 mg and in Duloxetine 40 mg in comparison to placebo for providing post operative analgesia.

Keywords: Duloxetine, postoperative pain, spine surgery

Introduction

Spine surgery is a major orthopedic procedure, often resulting in severe acute post-operative pain, which has been challenging to manage.

Inadequate management of postoperative pain in first 48 hrs after the surgery has been shown to increase the risk of Chronic Post Surgical Pain (CPSP).For an early postoperative recovery it is essential to achieve adequate postoperative pain management. So the primary aim of postoperative pain management is to provide adequate pain relief with minimum medication and to reduce any possible side effects of the administered drugs[1]. Negative clinical outcomes of inadequate postoperative pain management such as tachycardia, hypertension, decrease in vital capacity and alveolar ventilation, pneumonia, insomnia, myocardial ischemia, myocardial infarction, poor wound healing and transition to chronic pain have been observed in various studies[2]. Inadequate postoperative pain relief leading to increase in incidence of prolonged post-anesthesia care unit (PACU) stays, late hospital discharge, and unanticipated admission following ambulatory surgery or readmissions have been recorded in numerous studies[3].

In spinal decompression surgery, surgical tissue injury to soft tissues and bony structures results in nociceptive pain, in addition to neuropathic pain resulting from manipulation of neurological tissue[4].Surgical incision leads to central sensitization which results in significant postoperative pain. To prevent establishment of altered central processing, analgesic treatment can be given which results in reduction of acute postoperative pain and chronic pain development[5].

Opioids remains mainstay for treatment of moderate to severe postoperative pain but its chronic use increases the risk of perioperative opioids induced hyperalgesia and chronic post surgical pain[1,7].Analgesic adjuncts other than opioids are used in combination to decrease opioid consumption as well as opioid-related side effects in postoperative period. The use of adjuncts with opioids, necessitates to be aware of their dose-response relationship in order to optimize their analgesic efficacy and to reduce side effects from their combination[5].

Multimodal analgesia combining opioids and non-opioids aims to manage postoperative pain arising from various sites in the central and peripheral nervous system[6]. Some of the adjuvants which have proven to be useful in perioperative pain management are ketamine, gabapentanoids (gabapentin,pregabalin) and clonidine[6,7].

Duloxetine (SSNRI) was introduced in the field of pain management as an adjuvant, pertaining to its antinociceptive effect and ability to modulate pain pathways as it could interfere with chronic post surgical pain occurrence[1]. SSNRI antidepressants have been shown to provide varying degrees of pain relief in various chronic pain syndromes including post herpetic neuralgia, diabetic neuropathy, and fibromyalgia.As the role of duloxetine in acute pain has not been explored so far, therefore duloxetine may play an uncharacterized role in reducing acute postoperative pain as well as reducing dose of analgesic consumption[6]. So far, studies have been done with the

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use of single dose of duloxetine for postoperative pain relief; but none has been done so far for use of duloxetine in different doses.
Therefore the present study has been designed to evaluatethe efficacy of duloxetine in different doses for postoperative pain relief in patients undergoing lumbar spine surgery.

Material and methods

This study was approved by the ethics committee of G.R. Medical College, Gwalior (M.P.). The study was started in the Department of Anaesthesiology, J.A. Group of Hospitals Gwalior (M.P.) during February 2018 to September 2019 after getting written informed consent from the patients. All patients underwent lumbar spine surgery. Patients received duloxetine 60 mg, duloxetine 40 mg or identical placebo orally one hour before surgery, and the medication (duloxetine 40mg, 60mg or placebo) was administered again 24 hours later. The medication was administered by the nurses. The tablets were only identified by a number, which was only revealed at the end of the study by opening the packets in which it was registered whether it was duloxetine 60 mg, 40 mg or placebo. The substances (duloxetine 60mg, 40mg or placebo) were conditioned in 120 envelopes with 2 tablets each.Patients of ASA Physical Grade I and II between the age group 20 to 60 years of either sex were included. Exclusion Criteria were as follows: Patient's refusal,uncooperative patients /not able to understand pain assessment test,history of clinically significant cardiovascular, pulmonary, hepatic, renal, neurological, psychiatric, or metabolic disease,patients who are unable to understand NRS assessment,patients having severe obesity (BMI > 35 kg/m2), coagulation disorder, on anticoagulants, or any sensitivity to local anaesthetics, patients with history of drug allergy to duloxetine, paracetamol or tramadol ,drug addict / patient on long term steroid therapy,patients using antidepressants or anticonvulsants within 14 days of surgery,opioids within 24 hour before surgery.
The patients were randomly allocated into the following3 groups (n=40 each) Group I (control) included 40 participants who received a placebo tablet 1 hour before surgery and another tablet the following morning. Group II(duloxetine 40 mg) included 40 participants who received 40mg duloxetine 1 hour before surgery and again the following morning. Group III(duloxetine 60 mg) included 40 participants who received 60mg duloxetine 1 hour before surgery and again the following morning. Upon arrival of the patient in the operation room, intravenous access with 18G cannula was established and 500 mL of crystalloid infusion was started. All the baseline vital parameters like NIBP, pulse oximeter, electrocardioFigy using three lead ECG, were connected and basal reading recorded of pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate. Patients were preoxygenated with 100% oxygen for 3 minutes by facemask. All patients were uniformly premedicated with inj. Glycopyrrolate 0.005-0.01 mg/kg IV, inj. Pentazocine 0.3-0.6 mg/kg IV. Anaesthesia was induced with inj.Thiopentone 3-5 mg/kg IV. Endotracheal intubation was facilitated with i.v. Inj. Succinylcholine 1- 1.5mg/kg IV and IPPV was done for 60 seconds with 100% oxygen. Laryngoscopy was done with Macintosh blade laryngoscope and tracheal intubation done with appropriate sized cuffed endotracheal tube. Cuff was inflated and bilateral equal air entry was confirmed on both side of chest and then tube was fixed. Anaesthesia was maintained with N_2O: O_2 (67:33) and isoflurane gas mixture on Bain's anaesthetic circuit along with Loading and intermittent dosage of non-depolarizing muscle relaxant Inj. Atracurium Besylate 0.5 mg/kg IV loading dose followed by increment doses at 0.1 mg/kg IV was used to maintain general anaesthesia under controlled ventilation throughout the surgical procedure.No additional infusion of any opioids was given during the procedure. After completion of the surgery, neuromuscular blockade was reversed with inj. Neostigmine 0.04-0.08 mg/kg IV and inj. Glycopyrrolate 0.5mg IV once adequate reversal was obtained. Patient was shifted to postoperative ward for further monitoring.Postoperatively pulse rate, blood pressure, respiratory rate and severity of pain on NRS scale was noted at 1 hr, 6 hr, 12 hr, 24 hr and 48 hr after surgery. And the presence or absence of adverse effects, such as headache, nausea, vomiting, dizziness, and drowsiness were noted.Postoperatively, pain management consisted of intravenous paracetamol 1gm by infusion (100 ml over 30 minutes)every 8 hours, starting from 6th postoperative hours, for 48 hours after surgery. And tramadol 2 mg/kg IV was given as rescue analgesic whenever the subject requests for analgesic and when NRS ≥ 4.
The observations recorded in the three groups were tabulated and statistical analysis was carried out by using statistical software SPSS 20.0. Student 't' test for intra- group and inter group comparison was applied and $p>0.05$ and $p<0.05$ were considered as statistically insignificant and significant respectively.

Results

This study was started in January, 2018 at Jayarogya Hospital, Gwalior India and ended in September, 2019. There were no statistically significant difference between three study groups regarding demoFigic data such as age, weight, sex and duration of surgery (min) as shown in table 1.

Table 1: DemoFigic profile and duration of surgery among three groups

Parameters (Mean±SD)	Group I	Group II	Group III	p value
Age (yrs)	42.80±12.23	44.5±9.41	44.2± 9.80	0.740
Weight(in kgs)	60.22±8.87	58.2±7.44	60.68±8.22	0.344
Sex (M:F ratio)	2.63	2.07	1.85	0.764
Duration of surgery(min)	134±39.60	133±41.95	135±41.07	0.963

Time for rescue analgesia was significantly prolonged in both duloxetine 60mg (107.38±11.44) and duloxetine 40mg(78.13±14.49) as compared to placebo (38.13±8.37) and was higher in duloxetine 60mg as compared to duloxetine 40 mg (duloxetine 60 mg > duloxetine 40 mg > placebo).
On hemodynamic parameters, significant changes (mean difference $p<0.05$) were present at 1st hour in pulse rate, systolic blood pressure and diastolic blood pressure among three groups and non significant at all other points of time.NRS score were lower in both duloxetine 60 mg and duloxetine 40 mg as compared to placebo. NRS score in duloxetine 60mg was lowest but statistically non significant compared to duloxetine 40mg and placebo (placebo>duloxetine 40 mg>duloxetine 60 mg) at all the points of observations.
12(10%) patients suffered with nausea and vomiting, 5 (12.5%) patients in duloxetine 60 mg group and 5 (12.5%) in duloxetine 40mg group patients as compared to placebo group only 2(5%) patients.
In placebo group none of the patients had drowsiness, in duloxetine 60 mg 5(12.5%) patients had drowsiness, while in duloxetine 40mg, 4(10%) patients had drowsiness. Thus it was found that duloxetine causes more drowsiness than placebo.
11(9.16%) patients suffered with shivering 4(10%) patients in duloxetine 60 mg group, 3(7.5 %) in duloxetine 40mg group and 4(10%) in placebo group patients.
None of the patients in all the three groups has bradycardia/tachycardia, hypotension/hypertension, respiratory depression and headache.

Discussion

This is a study to assess the effect of short-term administration of duloxetine on acute postoperative pain in patients undergoing lumbar spine surgery under general anesthesia.
Duloxetine 60 mg is being used in chronic neuropathic pain. Dose less than 60 mg was not found to be effective in management of chronic neuropathic pain.

Selection of duloxetine 60 mg dose in our study was based on previous studies conducted by Hoi etal[7], Bedin et al[6] and Nasr DA[9] for acute post operative pain management. So we tried to study the efficacy of duloxetine 40 mg and 60 mg for acute postoperative pain management.Most of the previously done studies had not taken perioperative haemodynamic variables into consideration Postoperative hemodynamic variables of intra-group and inter-group statistical analysis, significant difference was found at 1st post operative hour which might be related to haemodynamic changes occurring during emergence from general anaesthesia. However at 6th, 12th, 24th and 48th postoperative hour no significant difference was found. Kassim D Y et al[5], studied on haemodynamic variables while comparing the analgesic efficacy of duloxetine (with or without dexamethsaone) with placebo for the first 12 postoperative hours, founda significant difference in heart rate and mean blood pressure during first 6 postoperative hours. Our results were in accordance with the study.

Our study showed a significant longer time to first rescue analgesic in the duloxetine 40 mg as well in the duloxetine 60 mg group than the control one as shown in Table no.2.

Table 2: Time for Rescue Analgesia (TRA)(Mean±SD) among the three groups

Parameter	Group I (n=40)	Group II (n=40)	Group III (n=40)	p value
TRA (mins)	38.13±8.37	78.13±14.49	107.38±11.44	<0.05

On comparison and application of statistical analysis (Table no.3), significant difference (p<0.05) was found while comparing placebo with Duloxetine 40mg , placebo with Duloxetine 60 mg and Duloxetine40mg with Duloxetine 60 mg. This might be due to the synergistic effect of duloxetine and the intraoperative used opioids as well as due to the potentiation of the action of intraoperative opioids by duloxetine which leads to prolonged time for first rescue analgesia. As selective norepinephrine reuptake inhibitors may significantly increase the intensity and duration of opioids antinociceptive activity via both α2-adrenergic and opioid receptors. Another study done by Siddiquea et al[8] showed that a combination of morphine and duloxetine produced a significant increase in reaction time suggesting additive antinociceptive action. Therefore combination therapy would theoretically minimize the dose requirements and thus the potential adverse effects of opioids.

Table 3 Inter group statistical analysis of Time for Rescue Analgesia (TRA) among three groups

Parameters	Group- I v/s II		Group - I v/s III		Group - II v/s III	
	t-value	p-value	t-value	p-value	t-value	p-value
TRA	-15.119	<0.05	-30.903	<0.05	-10.024	<0.05

Saoud A et al[4] supports our study in which they studied the efficacy of duloxetine 60mg and pethidine consumption in patients undergoing anterior cervical microdiscectomy and fusion. Similarly Nasr D.A[9]conducted a study in patients given perioperatively duloxetine 60 mg scheduled for radical mastectomy with axillary dissection and Altiparmak B et al[10]study to compare the effect of preoperative pregabalin or duloxetine on pain management and on cognitive functions after spinal surgery both found the same results as ours. Attia J Z et al[11] conducted a placebo controlled study to assess the effect of perioperative use of Duloxetine in combination with Etoricoxib on postoperative pain in patients scheduled for lumbar laminectomy, results were in accordance to our study.

Mean Numeric Rating Scale (NRS) score at different postoperative time interval in the three groups is shown in Fig 1.

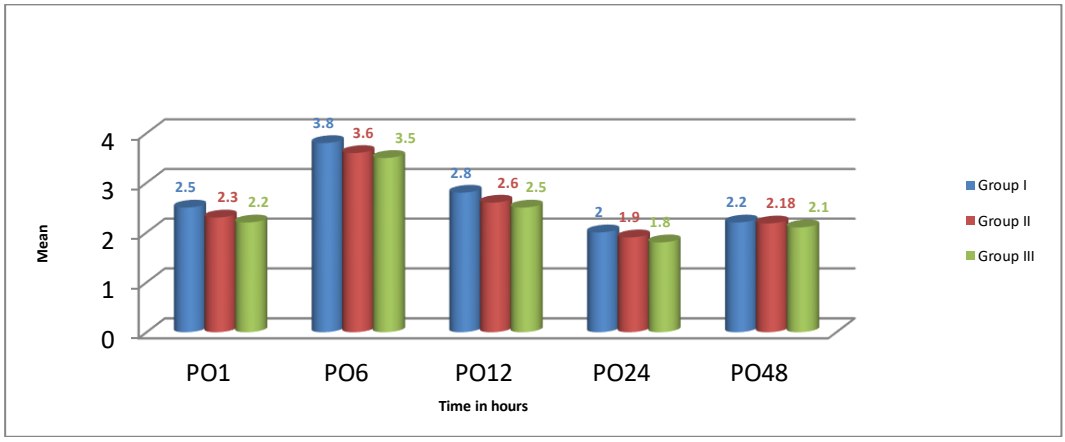

Fig 1:Mean Numeric Rating Scale(NRS) score at different time interval in the three groups

Duloxetine is a selective SNRI that is efficacious in chronic pain conditions such as painful diabetic neuropathy and fibromyalgia.The possible mechanism of action of duloxetine in our study could be explained by the central pain inhibitory action secondary to the potentiation of serotonergic and noradrenergic activities in the CNS. For ethical consideration, we did not allow patients to suffer pain with NRS≥4 and the mean NRS-pain scores in all the groups were approximately 3 throughout the entire study period. Any patients that suffered pain (NRS≥4) was offered rescue analgesia in form of tramadol 2mg/kg IV. However all patients were given intravenous paracetamol 1gm by infusion (100 ml over 30 minutes)every 8 hours, starting from 6th postoperative hours, for 48 hours after surgery for pain management. Thus we expected that all three groups shall show similar NRS scores with no statistically significant difference between the groups in this aspect. On statistical comparison of average NRS scores of 48 hours observation period, no significant difference (p>0.05) was seen in NRS scores at different point of time postoperatively among the study groups and all the three groups were comparable.

Few studies have evaluated the effect of duloxetine on pain scores in postoperative period. Bedin A et al[6] evaluated the efficacy of 60mg duloxetine in patients undergoing elective spine surgery, and Ho KY et al[7] performed the same evaluation in patients undergoing knee replacement surgery in whichthey found no significant difference between the groups in pain scores.

Likewise in the study by Saoud A et al[4], comparing preoperative use of duloxetine 60mg 2 weeks prior and 2 weeks after anterior cervical micro dissectomy with placebo, non-significantly lesser pain scores were found in duloxetine 60mg than in placebo. In contrast to our study, Alves C et al[12] reported significant pain scores postoperatively in patients after abdominal hysterectomy. And recently, study done by Altiparmak Bet al[10] found lower mean Visual Analogue Scale scores of the pregabalin and duloxetine groups in comparison to placebo group after spinal surgery Nasr D.A.[9] found lower VAS scores of pain in preoperatively administered duloxetine 60 mg compared with placebo group in patients undergoing radical mastectomy which does not coincides with our study. Attia J Z et al[11] studied the effect of preoperative duloxetine 60 mg and etoricoxib 120 mg in patients who underwent lumbar laminectomy, and the pain scores were lesser in duloxetine group in comparison to placebo at rest, at 24th at 48th hour which is against our results.As regard of postoperative adverse effect in the study, all cases of three groups were haemodynamically stable and study showed incidence of post operative nausea & vomiting and drowsiness were higher in duloxetine 60 mg and 40 mg when compared to placebo and incidence of shivering was almost similar with duloxetine and placebo among the three study groups during the study period as shown in Fig 2. Previous studies on duloxetine with placebo done by Saoud A et al[4],Altiparmak B et al[10],Kassim DY et al[5]and by Nasr DA[9] have demonstrated an increased incidence of nausea-vomiting and drowsiness in duloxetine group as compared to placebo but the difference was non significant.

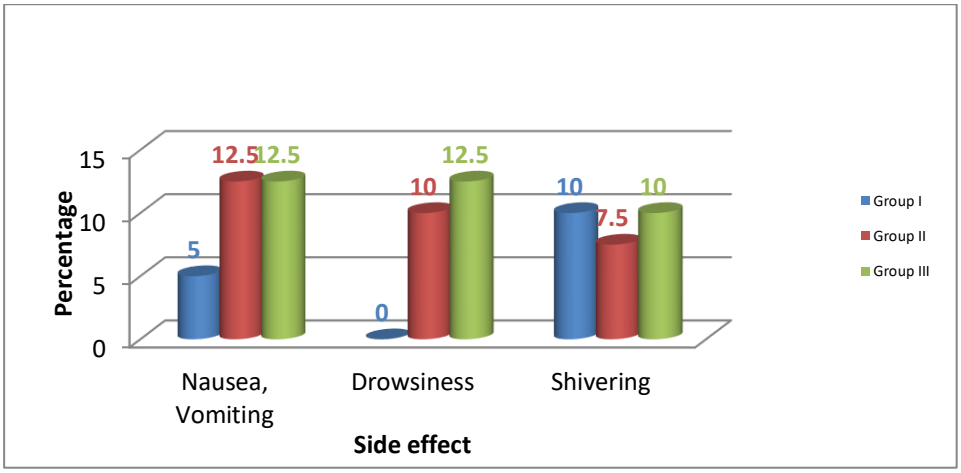

Fig 2:Different side effects and complications during study period

There are few limitations to our study. Firstly, the study lacks any information about the opioids sparing effect of duloxetine. The reason being our institutional pain management strategy. We prefer to use paracetamol infusion for postoperative pain management and tramadol for rescue analgesia instead of opioids.

We studied only the patients undergoing lumbar spine surgery and therefore, cannot generalize our finding to patients undergoing different surgical procedures. And lastly we have not evaluated the possible effect of duloxetine on chronic postsurgical pain**.**

Conclusion

In our study, patients receiving duloxetine 40 mg and 60 mg had a prolonged duration of 1st rescue analgesia than the placebo although pain scores did not differ significantly between the groups. Therefore, we suggest in our study that short-term duloxetine treatment may be a good adjuvant for decreasing the need for opioids in order to alleviate postoperative pain without significant adverse effects.

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