

**EVALUATION OF THE EFFICACY AND SAFETY OF ORAL PREGABALIN ON
REDUCTION OF POST LIGATURE HERNIORRHAPHY INTRAVENOUS
OPIOID CONSUMPTION, IN COMPARISON WITH CONTROL GROUP IN
ZANJAN AYATOLLAH MOUSAVI HOSPITAL, 2014-2015**

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ABSTRACT

Back ground and objective: Pregabalin, a GABA analog, shown to be effective in several models of neuropathic pain. We evaluated the efficacy of pregabalin in post herniorrhaphy intravenous opioid consumption.

Materials and Methods: Sixty male patients who were scheduled for unilateral inguinal herniorrhaphy were randomly allocated to two groups: the pregabalin group received single-dose 300 mg oral pregabalin 2 h before and 150 mg pregabalin 12 and 24 h after surgery in addition to routine medications including pethidine, and the control group just received routine medications. Postoperative pethidine consumption and the adverse effects of pregabalin were evaluated. Finally statistics analysis was done with SPSS 11.5 program and the results were presented.

Results: Compared with the control group, the pregabalin group displayed lower pain and Pethidine consumption after surgery. Pregabalin led to more somnolence and dizziness in compare to control group during first 12 h after surgery.

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Conclusion: Pregabalin lowered opioid consumption. With regard to adverse effects those are limited to first 12 h after surgery pregabalin can be suggested for pain relief but its usage in elderly patients should be warily.

Keywords: Pregabalin, inguinal hernia, Pethidine.

INTRODUCTION:

Inguinal hernia can be considered as congenital or acquired diseases. The most common cause of their development is the weakness of the muscular structure of the abdominal wall. There are several categorizations for it, but in general, the most common is indirect type. The current incidence of inguinal hernias is around 18% and the current risk of developing it over the lifetime is 26%, with an increase in prevalence with age (1).

There are various surgical procedures for the treatment of inguinal hernia, but currently the most commonly used methods are open procedures (86%) versus laparoscopic (14%) methods (1).

Hernia surgery can be accompanied by moderate to severe pain, which results in long-term hospital stay and a delay in returning to daily activities (2,3,4); This inactivity, particularly in the elderly As a risk factor for life threatening conditions, such as deep vein thrombosis and, ultimately, thromboembolism. From day to day, the tendency to use the mesh in the repair of the hernia increases with its lower relapse rate; about 10% of the patients suffer from chronic pain after surgery to repair the hernia with the mesh, and about one third of them limit the daily activity mentions of the same chronic pain (5). Some researchers believe that inadequate control of acute postoperative pain can be considered as a risk factor for chronic pain (2,6,7). Therefore, the proper control of postoperative pain was always considered by surgeons. Opioids are major maintenance treatments for controlling postoperative pain. Unfortunately, they have side effects such as nausea, vomiting and itching, urinary retention and, even in cases of respiratory depression, which limit their use and, therefore, use of other drugs along with those who use other mechanisms to control pain. (8); NSAIDs, paracetamol, low ketamine, and regional block are used; NSAIDs can lead to gastrointestinal bleeding. Ketamine has psychogenic effects; neuromuscular blocking techniques require additional intervention and are associated with a number of potential complications; therefore, a drug that does not have these complications is an attractive option (9, 10).

Administration of gabapentin and pregabalin is the forefront of the treatment of patients suffering from chronic neuropathic pain, and it is possible to control the incidence and severity of acute postoperative pain (11, 12).

Gabapentin is a structural analogue of GABA; pregabalin is structurally similar to gabapentin and has anti-seizure effects, anxiolytics and sleep regulation; such as gabapentin in different models of neuropathic pain (13), injuries of incisional (14) and injury Inflammatory is effective(15).

Researchers have found that gabapentin leads to reduced pain intensity, reduced opioid use and reduced unwanted side effects associated with opioid use (9).

Compared with gabapentin, pregabalin is more rapidly absorbed (1 hour versus 3 to 4 hours) and has a higher bioavailability (90% versus 33-66%). It also has an analgesic effect 3 to 4 times more than gabapentin (9).

Pregabalin is generally well tolerated and has mild to moderate side effects, which is dose dependent and seen at high doses; dizziness and drowsiness are the most common side effects that can be reversible when discontinued (9).

Pregabalin is more effective in controlling acute pain than gabapentin (11, 17).

In recent years, pregabalin has been used to control pain after laparoscopic surgery, outpatient surgeries and small gynecological procedures that have been effective in reducing pain, anxiety, and opioid use (9). However, there are few studies that evaluated its effect on acute pain control after the repair of the hernia with the mesh; it is recommended that further studies be conducted to evaluate the efficacy of pregabalin (18).

Most studies have been conducted to evaluate the effect of gabapentin on postoperative pain management, but there are few studies that have been designed specifically forHerniorrhaphy post-operative pain control. On the other hand, studies have shown that pregabalin, a structural analogue of gabapentin, is more effective onacute postoperative pain control than gabapentin, which is associated with fewer side effects (11, 17).

Two studies on the effect of gabapentinoids on postoperative pain are one study by Sen et al., Which evaluates the single dose of gabapentin 1200 mg and examines the pain of the first 24 hours after surgery, as well as chronic pain after surgery, gabapentin is considered more effective in reducing pain in both cases. Another study by Jacques is a multicentre study that evaluates the effects of pregabalin. Both of these studies have shown that gabapentinoids are effective in reducing the amount of analgesicsconsumption, such as tramadol, acetaminophen and oxycodone, but further studies have been suggested (18,20).

In this study, the effect of pregabalin, a newer drug than gabapentin, on the reduction of acute postoperative pain was studied;fewer studies have been conducted to investigate the effect of it after a herniorrhaphy. The pethidine consumption,commonly used drug to control pain in our surgical departments, and its possible side effects have been evaluated, as in previous

studies, tramadol, acetaminophen and morphine have been used. Considering the limited use of gabapentinoids and especially pregabalin by Iranian surgeons for the control of acute postoperative pain, it can be suggested to the surgeon to use it if the efficacy and safety are proven.

METHOD OF CONDUCTING RESEARCH:

This study was designed as a randomized clinical trial and was approved by the Ethics Committee with the code ZUMS.REC.2013.117. Patients referred to Ayatollah Mousavi Hospital in the year 2014 that had indirect inguinal hernia and candidates for surgery were included.

All patients underwent spinal anesthesia and Liechtenstein method by the same surgeon. Patients undergoing surgery for this emergency department or at the same time undergoing another surgery, or with evidence of diabetic, ulcerative, peptic ulcer, gastritis, renal failure, neurological diseases and neurological or abusive use of drugs materials were not included in the study; then patients were randomly assigned into two groups of case and control, using randomized packs.

In the case group, in addition to routine treatments, 300 mg of pregabalin (a biochemical company manufactured as 2 capsules of 150 mg) was given to the patients two hours before surgery, and these patients received 150 mg for 12 and 24 hours postoperatively. ; In the control group, only the routine treatments were taken at the above mentioned times; the amount of intravenous ingestion (1 mg pethidine per kg bodyweight at each time) was recorded and, after the operation, the oral NSAID value (number of 400 mg gelofen capsules The warmth of the Dana Pharmaceutical Company was recorded at home; Patients received training before completing the relevant form and were visited at the end of the first week after surgery by a surgeon that was not aware of the case or control, and the data was recorded and if patients were not contacted, they were contacted by phone and requested to register the contents of the form at home. Finally, the data collected by the SPSS11.5 statistical programs were reviewed and the findings were announced.

FINDINGS:

From September to February 2014, 60 patients with unilateral hemorrhage referred to Ayatollah Mousavi hospital in Zanjan who entered the study were enrolled in the study. They were randomly assigned into two groups' 30 interventions and controls were evaluated. After

discharge, three of the intervention group and two of the control group were excluded because of non-cooperation in postoperative follow-up.

The mean age of the patients and the mean time of surgery did not significantly differ with respect to P value more than 0.05. The average interval between the first requests for postoperative pain after the completion of the surgery was 7.07 hours in the intervention group and 5.15 hours in the control group. The resultant p.v = 0.054 is Borderline and therefore, since the value of Pi is very close to 0.05, it cannot be said with certainty that the difference is not meaningful. Patients in the intervening phase of the postoperative period went out and walked out and the difference was reported statistically significant (Table 1).

Table 1

	Intervention group average(Standard deviation)	Mean control group (SD)	P Value
Age	55.03 (17.2)	53.17 (20.12)	0.701
Average surgical time	67.5 (22)	70.83 (16.45)	0.5
The interval between the first request for accommodation	7.07 (3.78)	5.15 (3.24)	0.054
First time walking distance (hours)	7.1 (2.9)	9.3 (2.73)	0.004

The patient's pethidine levels were recorded in the first 24 hours and the total duration of admission. In the first 24 hours, 5 patients in the intervention group did not receive any pethidine treatment. 16 subjects received 1 dose and 9 received 2 doses of pethidine in total. Pethidine was administered in 2 groups; 9 received 1 dose, 14 received 2 doses, 5 received 3

doses, and 52 received pethidine. In general, the group received less pethidine, which is statistically significant ($P < 0.05$) due to P value less than 0.05 (Fig. 2).

The intervention group received an average of 2.2 days and the control group was 2.37 days in the hospital. The difference was statistically meaningless ($p = 0.190$). Patients in the intervention group received less gelofen compared to the control group until day 3 and in total 7 days after surgery. (Table 2)

Table 2. Number of patients taking gelofen

	Until the third day Mean (sd)	Until seventh day Mean (sd)	P Value
Intervention group	3.96 (2.00)	7.39 (3.87)	0.011
Control group	6.30 (1.79)	10.04 (3.60)	

Drug side effects such as nausea and vomiting, dizziness, headache, drowsiness, urinary retention, dry mouth, blurred vision, drowsiness, itching, hypotension and constipation in the first 12 and 24 hours after the operation, as well as on days 3 and 7 after the operation it placed. From the complications of the study, both intervention and control groups experienced complications such as nausea and vomiting, headache, dizziness, drowsiness and urinary retention in the first 12 hours after operation, and one in the intervention group also suffered from hypotension. Regarding the statistical analysis and the P value less than 0.05, the difference between the incidence of dizziness and drowsiness can be attributed to pregabalin, but the other complications were not statistically significant. In the 12 hours after the operation, complications such as nausea and vomiting, dizziness, headache, drowsiness and urinary retention were observed in both intervention and control groups, which were not statistically significant (Table 3).

On the third day after surgery, only one out of 27 survivors of the control group mentioned the headache and none of the 28 intervention group had experienced headache. The remaining side effects were not seen and the difference was not statistically significant. On the seventh day after the operation, none of the subjects in the intervention or control group reported any complications.

Table 3. The incidence of drug complications in the intervention and control group in the first 12 hours after the operation

		Nausea vomiting	Dizziness	Headache	Drowsiness	Urinary retention	Hypotension
Intervention group	The first 12 hours	26.7%	23.3%	20%	26.7%	13.3%	3.3%
	12second hour	16.7%	3.3%	10%	6.7%	3.3%	0
Control group	The first 12 hours	16.7%	3.3%	13.3%	6.7%	13.3%	0
	12second hour	16.7%	3.3%	10%	6.7%	3.3%	0
P.V	The first 12 hours	0.347	0.023	0.488	0.38	1	1
	12second hour	0.085	1	1	1	1	1

DISCUSS

According to the obtained data and statistical analysis, it seems that pregabalin drug significantly reduces pethidine consumption during the admission period.

Sixty patients were enrolled in the study to prevent gender-disruptive effects on all male patients. The two interventions and control groups had mean age of 55.03 and 53.17 years, respectively, which, due to the P value, was less than 0.05, the age-related effect of aging was eliminated. All patients underwent spinal anesthesia by surgery and the same surgical technique. The duration of surgery in the two groups did not differ significantly with respect to P value more than 0.05, and the effect of the confounding of these factors was also eliminated.

The amount of pethidine consumed in the first 24 hours, as well as the length of the hospitalization period, according to the P value of 0.023, was lower in the intervention group and it is in the interest of pregabalin to reduce the use of pethidine in patients. Studies by Sen and Jacques have also shown a similar effect; the studies used in this study included tramadol, morphine, and acetaminophen.

After discharge from the hospital for the control of pain at home, patients were prescribed gelofen capsule. Results showed that pregabalin significantly reduced the use of housing until the third day and until the seventh day in the home, but considering the average consumption of The 4th to 7th day in the intervention and control groups was 3.43 and 3.74, respectively. It seems that the difference in 7-day oral administration is more due to the difference in consumption in the first 3 days and pregabalin on the consumption of oral hygiene from day 4 to 7 have no special effect. The study did not evaluate the amount of oral home-based home care, and Jacques's study reported a cumulative amount of opioids in the first 7 days after surgery in less pregabalin patients.

In postoperative complications, complications such as nausea, drowsiness, dizziness, headache and urinary retention were seen in the first 24 hours after surgery, and one of the recipients of pregabalin also had hypotension in the first 12 hours. Only the occurrence of drowsiness and dizziness during the first 12 hours after the operation was statistically significant and can be attributed to the use of pregabalin for these two complications. In the study of Sen, the incidence of complications is mild and insignificant, only nausea and vomiting, and hypotension and bradycardia have been mentioned. Of course, the study group was in the age range of 20 to 40 years old, while the average age of our study was about 55 years and the incidence of these complications is more common in older ages. In the Jacques study, related side effects include nausea, drowsiness, dizziness, and constipation. Both of these studies did not mention the incidence of these complications.

CONCLUSION

In summary, the results of the study can be summarized as follows: the use of pregabalin 300 mg two hours before and 150 mg, 12, and 24 hours after herniorrhaphysurgery led to a decrease in the use of pethidine in the first 24 hours and The duration of hospitalization, leaving the bed and walking early after the operation and reducing the consumption of oral NSAIDs at home, but with increasing incidence of dizziness and drowsiness in the first 12 hours after surgery, is associated with elderly patients.

Therefore, taking into account the benefits of less consumption of opioids and earlier withdrawal from the bed and walking, and due to the limited complications mentioned in the postoperative period, it can be selected selectively in the control of pain after inguinal herniorrhaphy. Long-term studies are recommended to evaluate the effect of pregabalin on chronic pain after surgery. Projections of other studies with less pregabalin doses may lead to less complication postoperatively, so other studies may be useful in this regard.

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