

Acute pain management in laparoscopic cholecystectomy: Is there a role for pregabalin? A review

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ABSTRACT

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A review.

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Postoperative pain management has become pre-requisite for early recovery after laparoscopic cholecystectomy and the ideal management of it is definitely multimodal due to the complexity of its nature. Many analgesic approaches have already been tested to relieve pain after laparoscopic cholecystectomy and anticonvulsants drugs, like pregabalin and gabapentin might be useful and effective. Pregabalin is an antiepileptic drug that is often used to treat neuropathic pain. The use of pregabalin as part of multimodal analgesia is still under evaluation and may have a role in the postoperative management, as an adjunct. Several studies have evaluated the efficacy and adverse effects of pregabalin in reducing postoperative pain and opioid consumption. In this review, we discuss the role of pregabalin in acute postoperative management after laparoscopic cholecystectomy. Based on available clinical trials it is difficult to draw solid conclusions. More studies and especially well designed clinical trials are required in order to clarify the optimal dose and the duration of therapy before adopting pregabalin in routine clinical practice.

INTRODUCTION

Laparoscopic cholecystectomy is generally associated with significantly less pain compared to open approach. However, pain is not completely abolished after laparoscopy and still re-

mains a challenge in daily clinical practice, since 80% of patients will require opioid analgesia^{1,2}. Indeed, pain after laparoscopic cholecystectomy is a dominant complaint and the main reason for overnight in hospital after surgery. Etiology of pain is multifactorial and has several components: incisional, local visceral, peritoneal and referred to the shoulder tip, a

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characteristic feature, usually to the right side or to the back. Pain arises from the incision and trocar sites (50%-70%), the intra-abdominal trauma (10%-20%) and from the rapid distension of peritoneum (20%-30%) with traumatic traction on vessels and nerves, irritation of phrenic nerve and is associated with the release of inflammatory mediators³. It varies in severity, duration and character, although the first 12 hours is the period in which most of the patients report the worst pain. Acute pain after laparoscopic cholecystectomy reaches a maximum level within the first 6 postoperative hours. Shoulder pain is usually mild in intensity and remains for 24 hours^{4,5}.

Several analgesic interventions with different targets and mechanisms have been investigated for their influence on postoperative pain after the procedure (incisional infiltration or intraperitoneal installation of local anesthetics, NSAIDs, COX-2 inhibitors, steroids, epidural anesthesia, opioids, transversus abdominis plane (TAP) block)^{1,4}. Most of them are recommended from the procedure specific postoperative management (PROSPECT) Working Group for pain control in laparoscopic cholecystectomy^{1,4,6,7}.

Effective pain management improves quality of life and is a prerequisite in order to harvest the maximum benefits of minimally invasive surgery such as reduced length of hospital stay, faster recovery and earlier return to daily

activities and work. The ideal management of postoperative pain after laparoscopic cholecystectomy is definitely multimodal. The PROSPECT group has recommended that gabapentin can be used as an adjuvant for pain control after laparoscopic cholecystectomy. There is now considerable interest in the potential use of pregabalin as an analgesic adjuvant as a part of a multimodal analgesia for acute postoperative pain relief^{1,4,7,8}.

Pregabalin

Pregabalin, like gabapentin, is an amino acid derivative of gamma-amino butyric acid (GABA) analogue. It is an anticonvulsant drug used in epilepsy, but has already been used for chronic neuropathy pain, as well. In Europe, pregabalin has also been accepted in the treatment of anxiety disorders⁹. Both drugs (pregabalin and gabapentin) share a similar mechanism of action: Bind to the $\alpha 2\delta$ (alpha2delta) subunit of the voltage-dependent calcium channel in the central nervous system and modulate calcium influx as well as GABAergic neurotransmission. Pregabalin decreases the release of neurotransmitters such as glutamate, noradrenaline, and substance P. On the other hand, pregabalin increases neuronal GABA levels by producing a dose-dependent increase in glutamic acid decarboxylase activity (GAD). The latter is the enzyme that converts the excitatory neurotransmitter glutamate into the inhibitory GABA in a single step. For this reason,

pregabalin greatly potentiates benzodiazepines, barbiturates and other depressants. This mode of action translates into anti-epileptic, analgesic and anti-anxious effects. Sensitization of dorsal horn neurons, a mechanism involved in neuropathic pain has been demonstrated in acute pain models and may play a role in the development of chronic pain after surgery. By reducing the hyper-sensitivity of dorsal horn neurons induced by tissue damage, pregabalin may have a role in the treatment of postoperative pain.

Pregabalin absorbed with maximum plasma concentration within 1 hour, its oral bioavailability exceeds 90% and is independent of dose, which may produce a more predictable response of the patient. The elimination half-life ranges from 4-7 hours and is independent of dose and repeated dose administration. It is excreted by the kidneys and 98 % of the absorbed dose is excreted unchanged in the urine. Pregabalin elimination is nearly proportional to creatinine clearance and reduced in patients with impaired renal function.

Usual effective dose is 150-600 mg / day with an 8-12h interval between doses and the maximum daily dose of 600 mg. The side effects are mild to moderate, transient and dose-dependent. The most common side effects are dizziness and fatigue. Other common side effects are: dry mouth, blurred vision, double

vision, difficulty concentrating, increased appetite^{9,10}.

METHODS

Randomized controlled trials (RCT's) that assessed the effects of pregabalin on acute postoperative pain in humans after laparoscopic cholecystectomy and they were published between 2000 and 2015 were searched in Pubmed, Medline, Scopus and Cochrane library using the following key words: "pregabalin", "postoperative pain", "laparoscopic cholecystectomy", "analgesia". Only randomized placebo controlled trials published in the English language were included. Additional studies from reviews were also identified. Pain assessment, postoperative opioid consumption and side effects were considered the most important outcomes. The last electronic search was performed in June 2015.

A total of 6 RCT's including the use of perioperative pregabalin for the treatment of postoperative pain after laparoscopic cholecystectomy. Doses of pregabalin ranged from 50-600 mg and were administered as a single dose preoperatively or as multiple doses perioperatively (Table 1).

Pregabalin as a single dose preoperatively

Agarwal et al. used a single dose of 150 mg of pregabalin one hour preoperatively. They reported a statistically significant decrease in pain intensity (static and dynamic) with pregabalin compared to placebo in the late post-

operative period (24hrs). A reduction was also recorded in total patient controlled analgesia (PCA) fentanyl consumption in the pregabalin group compared to placebo group. There was no difference between pregabalin and placebo groups for adverse effects such as nausea, vomiting, headache, respiratory depression¹¹.

In another placebo controlled double blind RCT Balaban et al showed that preoperative administration of PG 150mg and 300 mg one hour prior to laparoscopic cholecystectomy resulted in superior analgesia compared with placebo at Postanesthesia Care Unit (PACU). A dose of 300mg PG offered better analgesia than placebo 2 hours post-surgery, and 300 mg offered better analgesia than 150 mg 1hour after the procedure. In case of VAS > 5, 25µg of fentanyl was administered intravenously and repeated as required. Total intravenous (i.v) fentanyl consumption was higher in placebo compared to pregabalin groups. There was a reduction in fentanyl consumption, especially in group of patients received pregabalin 300 mg for the first 30 minutes. There were no differences between the groups in side effects such as nausea vomiting pruritus, urinary retention and they didn't observe side effects of pregabalin¹².

Our team demonstrated that pre-emptive analgesia with high dose of PG 300 mg twice (one dose of 300 mg the night before surgery and another 300 mg 1 hour prior to surgery) re-

duced early postsurgical pain at rest, particularly during movement and postoperative morphine consumption in patients undergoing laparoscopic cholecystectomy during the first 24 hours after the procedure. It is remarkable that 25% of patients in the PG group needed no additional analgesia with the PCA pump throughout the 24 hours. Side effects were similar among the two groups (vomiting headache, itching, sedation and respiratory depression, pain shoulder lack of concentration, blurred vision, weakness) except the incidence of dizziness which was significantly higher in the PG group during the first 8 hours post-operatively and occurred in 70% of patients. Patients receiving pregabalin exhibited a significant extubation time delay. This variable has not been evaluated in previous studies, so it is not known if it is a constant consequence or represents a dose-related effect¹³.

Two out of 3 trials used the PCA pump for postoperative analgesia which is an effective and efficient method of controlling severe acute pain. PCA offers advantages especially when protocols are in place to assess the level of pain and sedation. PCA administer more frequent but smaller doses of analgesia to patients, compared to the traditional nurse administered larger and less frequent doses. Busy hospital wards, number of staff, lack of knowledge regarding analgesic pharmacodynamics, overconcern about respiratory depression, long

period between the onset of pain and the administration of opioids may result in limiting the efficacy of traditional nurse-administered pain relief^{14,15}.

Table 1. Studies including pregabalin in acute pain management of laparoscopic cholecystectomy

	Pts(N) pre-gabalin/ placebo	Dose of pre-gabalin (mg)	Time of administration	Intra-operative analgesia	Postoperative analgesia	Assessment of APP	Adverse effects
Chang 2009	39/38	300	1 h before surgery and 12 h after initial dose	Pethidine 25mg I.V	ketorolac 30 mg I.V (at patient request)	48 h (static)	Increased sedation in pre-gabalin group
Peng 2010	48/48	50 or 75	1 h before surgery, 12 h and 24 h after the surgery	Fentanyl 2-5µg/kg Local anesthetic Intraoperative and port sites	Fentanyl 25-50 µg I.V every 5-10 min (according to patients comfort)	2 h (dynamic) (7 days at rest)	NS
Balaban 2012	30/30	150 or 300	1 h before surgery	Fentanyl 1.5µg/kg	Fentanyl 25 µg I.V (VAS≥5)	24 h (static)	NS
Sarakatsianou 2013	20/20	600 (2 doses)	Night before surgery and 1 h before surgery	Fentanyl 3-6µg/kg Apotel 1gr I.V	PCA morphine I.V (Activate dose=0.5mg lock-out=15min max.dose=1.2mg in 4h) Paracetamol every 8 h	24 h (static and dynamic)	Increased dizziness in pre-gabalin group
Bekawi 2014	30/30	150 mg	2 h before surgery, 12h after the surgery and twice a day for two days	Fentanyl 1µg/kg	Pethidine 1mg/kg IM (VAS≥3 or at patient request) Diclofenac 75mg IM (VAS≥4 or at patient request)	24 h	NS

NS:non significant, APP:acute postoperative pain, pts:patients,

N:number

Pregabalin given as multiple doses perioperatively

Three studies use pregabalin in different doses perioperatively. In a placebo controlled double blind RCT, patients divided in three groups in order to receive pregabalin 75 mg or pregabalin 50mg or placebo 1h before the procedure

and then 12 and 24h after the first dose. Peng et al reported that, multiple doses of PG 50 mg and 75 mg during laparoscopic cholecystectomy resulted in superior analgesia over placebo, but only for the first 90 minutes after day case laparoscopic cholecystectomy. A dose of 75 mg offered better analgesia than 50 mg and placebo and pain scores with movement were lower in the first 45 min after the procedure. However, pregabalin did not result in reduction in opioid consumption. Side effects were similar among the three groups¹⁶.

On the other hand Chang et al mentioned that perioperative use of pregabalin in two doses of 150mg 1 hour before surgery and then 12 hours after the first dose did not decrease the frequency or severity of shoulder pain as well as the severity of pain after laparoscopic cholecystectomy. Pain scores, time for first rescue analgesia and additional need of ketorolac consumption did not differ significantly in both groups Side effects were similar in both groups (nausea, vomiting, dry mouth, lack of concentration, blurred vision). Pregabalin associated with an increased incidence of sedation in the early postoperative period¹⁷. Moreover, Bekawiet all¹⁸ performed a randomized placebo controlled study comparing pregabalin 150 mg with placebo, administered 2 hours before surgery, 12 hours postoperatively and twice daily for 2 days. They concluded that 150 mg pregabalin perioperatively is effective

tive in reducing postoperative pethidine consumption without increasing the side effect profile, although it has failed to reduce postoperative pain (VAS scores). Author's explanation for this is that they had used an intermediate dose of pregabalin over an extended period and a single dose in order to decrease the side effect potential.

Also it is remarkable that this is the only study that used intramuscular (IM) opioid injection for pain control. This method is the most frequently used method for managing pain in the early postoperative period even though it has estimated that the IM "pro re nata" (prn) approach leaves almost the 50% of patients with unrelieved pain due to undermedication¹⁹ and in our opinion it is not a reliable method when protocols are in place to assess the level of pain, opioid consumption and sedation.

DISCUSSION

Based on available data from RCT's and reviews and due to the heterogeneity of data a conclusion cannot be drawn. Multiple doses of pregabalin 50-70 mg perioperatively failed to provide a reduction on opioid consumption but result in better analgesia in the early postoperative period. Pregabalin 300mg perioperatively associated with an increased incidence of sedation in the early postoperative period but did not result in reduction on postoperative

pain and opioid consumption after laparoscopic cholecystectomy.

Preoperative use of pregabalin 150 mg may be effective in reducing postoperative pain and fentanyl consumption in patients undergoing laparoscopic cholecystectomy with no additional adverse effects. In addition, pregabalin 600mg could play a role as premedication and as a part of a multimodal approach to acute postoperative pain management after laparoscopic cholecystectomy, although it is associated with an increased incidence of dizziness. The most frequently reported adverse effect of pregabalin which is transient and dose dependent.

A recent review from Cochrane Collaboration does not recommend the routine use of these pharmacological agents, like pregabalin, for postoperative management in people undergoing laparoscopic cholecystectomy²⁰. Similarly, a previous Cochrane review in 2009 on the effect of pregabalin on acute and chronic pain in a variety of procedures included six clinical trials with perioperative use of pregabalin and authors concluded that there is no evidence to support the use of pregabalin in acute pain²¹. According to a recent meta-analysis included 11 RCT's pregabalin failed to demonstrate significant reduction in postoperative pain; however, it reduced significantly opioid consumption and opioid-related adverse effects

during the early postoperative period (within 24 hours after the procedure)²².

Engleman et al. in their meta-analysis included 18 RCT's with patients undergoing surgery under general or spinal anesthesia concluded that pregabalin during a short perioperative period provides additional analgesia and decreased opioid consumption. Dizziness or light-headedness and visual disturbances were increased in the pregabalin group. There was no difference in the rate of sedation or lack of concentration and confusion between groups²³.

In a review by Durkin et al or 11 randomized controlled trials, they concluded that pregabalin may reduce perioperative opioid use in patients with more acute neuropathic pain than acute inflammatory pain²⁴.

Also, Eipe et al in their meta-analysis conclude that pregabalin appears to provide maximal benefit in procedures associated with neuropathic pain, but patients often experienced sedation and blurred vision, well known adverse effects of pregabalin²⁵.

The reasons for these contrasting results should be sought obviously in trials design and quality, different dosage schemes and duration of treatment, different anesthetic and analgesic techniques that have been used, outcome measures used population of patients and the broad variety of surgical procedures.

All this results should interpreted with caution, as there were only a few studies evaluating the

role of pregabalin in acute pain management after laparoscopic cholecystectomy, with small number of patients and many methodological differences.

These small size studies showed considerable heterogeneity in the dose of pregabalin, in the duration of treatment and the analgesic scheme. All these could be the reason for inconclusive results.

Under these circumstances a recommendation cannot be made on any specific dose and duration of treatment with pregabalin for acute pain management in laparoscopic cholecystectomy. Future efforts must be directed to multicenter well designed clinical trials of pregabalin in laparoscopic cholecystectomy with evaluation also of any possible effects on quality of life, return to normal activity and to work.

Many questions awaiting a clear answer: Which kind of patients may be benefit from pregabalin? What are the optimal dose and the duration of therapy? When should be administered? How does preoperative use of pregabalin interact with anesthetics and analgesics agents? How does pregabalin interact with opioid and non-opioid analgesics at postoperative multimodal pain management? There are serious drug-related adverse effects? How does pregabalin affect the recovery of patients? Could pregabalin have a role in one day laparoscopic cholecystectomy? Can pregabalin

reduce the severity or incidence of post-laparoscopic cholecystectomy syndrome?

CONCLUSION

In conclusion there is no clear evidence that perioperative use of pregabalin reduces post-operative pain after laparoscopic cholecystectomy and has opioid sparing effects. More well designed studies and trials are required in order to clarify the optimal dose, the duration of therapy, the benefits and risks, before adopting pregabalin in routine clinical practice in patients undergoing laparoscopic cholecystectomy.

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