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Evaluation of pregabaline efficiency in reducing opioid use and pain in post-operating patients subject to total knee arthroplasty surgery

Research Article

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Abstract

Total knee arthroplasty (TKA) is a very efficient surgical process in the treatment of degenerative knee changes. However, this procedure involves extensive tissue trauma, which contributes to the occurrence of severe postoperative pain. In this sense, pregabalin seems to be effective when administered before surgery with significant pain reduction and consequently the amount of opioid used postoperatively. Considering the importance of the subject and considering that there is no work in Alagoas and / or Northeast Brazilian populations that justifies the advantages of using Pregabalin in the preoperative period of TKA, this study aims to gather information collected from patients operated at Santa Casa de Misericórdia de Maceió in a period of one year. Thirty-six patients were studied during the research, where four were excluded due to data collection failure. The main indications for TKA were 2 patients with rheumatoid arthritis, 16 with arthrosis and 13 with refractory pain. In this context, pregabalin has recognized side effects, but in the study it was observed safety in the administration of this drug in the patient group 24 hours before the surgical procedure compared to the patient group 1 hour earlier as shown in Table 1. A greater reduction was observed. of pain according to VAS pain 24 and 48 hours after surgery, in the pregabalin group 24 hours before, in relation to the others. No decrease in postoperative opiod use was observed, as no study group achieved a VAS pain lower than 3 points over the length of stay. Therefore, a larger study with larger patient samples and case-controls is needed to obtain significant results.

Key words: Total knee arthroplasty, pregabalin, opioid, postoperative, Placebo

Introduction

Total knee arthroplasty (TKA) is a highly successful operation in the treatment of degenerative knee changes and is in increasing demand worldwide due to the aging population and the need to preserve people's quality of life. However, it involves extensive tissue trauma, which contributes to the occurrence of severe postoperative pain, and analgesia in this phase is of fundamental importance [1].

Approximately half of patients undergoing TKA experience severe pain after the procedure. Postoperative pain not only represents a time of physical and emotional distress, but also negatively affects patient recovery [2]. As with inflammatory metabolic endocrine response secondary to surgical trauma, untreated or inadequately treated pain leads to changes in the endocrine, cardiovascular, and central, peripheral, and sympathetic nervous systems. There is release of catabolic hormones such as cortisol, glucagon, growth hormone, endogenous catecholamines and inflammatory cytokines resulting in immunological impairment [3].

We can also cite for example increased oxygen demand and increased pressure on the cardiovascular system, which may then be associated with serious complications including ischemic cardiac events and myocardial insufficiency, which results in increased pressure on the arterial system [4]. In addition, pain immobilization may increase the risk of reduced lung function, gastrointestinal complications, and thrombus formation that are related to surgical stress [5].

In particular, such complications may negatively affect the mental status of elderly patients, causing delirium and / or anxiety. In addition, severe uncontrolled immediate postoperative pain may progress to chronic pain due to sensitization of the nervous system (AUBRUN et al., 2000). Thus, early rehabilitation and recovery may be delayed, resulting in longer hospital stays and increased hospital costs [6-10].

Faced with this problem, adequate pain management after TKA has been sought. It is not just for the human purpose of releasing patients from suffering, but is essential for success in terms of improving patient satisfaction, quality of life and preventing complications. The most important concept of current pain management after TKA is preventive use through a multimodal approach [11].

"Preference" refers to initiating pain management prior to surgical stimuli. In addition, "multimodal approach" means more than 2 drugs or modalities with different mechanisms or sites for synergistic effects. These two concepts are also known to be extremely effective in reducing opioid consumption, which has been associated with high complication rates [12].

Recently, several guidelines for postoperative pain management have emerged, one of which recommends the use of pregabalin as part of a multimodal regimen in patients undergoing surgery. This drug is associated with a reduced need for opioids after any surgical procedure, and some studies have reported lower incidence of postoperative pain [13].

Pregabalin has hyperanalgesic action in humans and is also used to treat chronic neuropathic pain [14]. Also, when used preoperatively, it can play a role in preventing acute pain from developing in chronic pain [15]. Although pregabalin was initially identified as treatments for neuropathic pain and other neurological disorders, several recent comments have revealed that pregabalin also reduces postoperative opioid consumption and improves pain levels after spinal surgery, laparoscopic surgery and thyroidectomy [16]. Thus, there are no comprehensive data regarding the analgesic efficacy of pregabalin in patients undergoing TKA [17].

In this sense, pregabalin appears to be effective when administered at a preoperative dose of 150 to 300 mg, one to two hours before surgery. Although some trials have also tested regimens including postoperative dosing, proving to be equally effective, typically using pregabalin 150 to 300 mg after 12 hours of the procedure [18].

This study gathered information collected from patients who underwent surgery and who participated in 3 intervention groups: pregabalin 1 hour before and placebo 24 hours before; pregabalin 24 hours before the procedure and placebo 1h before; placebo 1h and 24h before; being analyzed using pain assessment scales.

Methods

Design

Randomized clinical trial.

Local

Orthopedics and Traumatology Service of the Santa Casa de Misericórdia Maceió.

Sample

The sampling was done by convenience, inviting all patients submitted to total knee arthroplasty at the Santa Casa de Misericórdia de Maceió from August 2018 to May 2019.

Sampling

Patients who underwent surgical treatment of total knee arthroplast (TKA) within one year from the month of AUGUST 2018, who meet the inclusion criteria mentioned

in item 3.4.1, and agree to participate in the research according to Informed Consent (IC), being submitted for evaluation according to the VAS and an adverse effects questionnaire.

Inclusion Criteria

- Patients with knee gonarthrosis who underwent surgical intervention for total knee arthroplasty.
- Over 50 years at the time of surgery.

Exclusion Criteria

- Patients undergoing total knee arthroplasty for any indication other than gonarthrosis.
- Known or suspected sensitivity or contraindication to pregabalin. Pacientes com hipersensibilidade a dipirona e tramadol conjuntamente.
- Patients who have a neuro-cognitive disorder that prevents them from communicating with interviewers.
- Patients with rare hereditary problems of galactose intolerance, Lactase deficiency, Lapp deficiency or glucose-galactose malabsorption.
- Patients with heart problems, edema, renal failure, uncontrolled hypertension or hyperaldosteronism.

Methodological Procedures

After the consent of the informed consent, the patients received a brief explanation about the criteria that will evaluate the postoperative period of the surgery to which it was submitted and about the questionnaires to be applied.

Pregabalin and sodium bicarbonate hypersensitivity tests were performed, with the permission of the patient who wishes to volunteer the research, during the preoperative consultations, before ingestion of these drugs.

Eligible patients were randomized into three groups, two intervention groups and one control group, using the Random Allocation Software version 1.0 program. Group 01 patients received placebo 24 hours before surgery and pregabalin one hour before surgery. Group 02 patients received pregabalin tablet 24h before and placebo tablet 1 hour before the surgical procedure. Patients in group 03, control group, received the placebo tablet 24 hours before surgery and placebo 1h before surgery (annex 1).

Subjects from the experimental group received pregabalin at a dosage of 300mg. In the control groups a tablet containing sodium bicarbonate of the same color, size, shape and weight as pregabalin tablets will serve as a placebo. A researcher B, who is unaware of the result of randomization, will administer the pills after being directed by researcher A, who consulting the list of random numbers defines which group the patient belongs to. Another blind C researcher was responsible for the outcome assessment (annex 2).

All groups underwent arthroplasty under spinal anesthesia with 20mg isobaric bupvacaine and at the end of the procedure, femoral nerve block with 0.25% levobupivacaine was performed to complement the analgesia.

The surgical technique of total knee prosthesis is described in annex 3.

Statistical analysis of the data was performed by the program in Epi-Info ;7.1 and then a profile of the patients was drawn and the data distributed in tables and graphs of descriptive statistics, in order to allow analysis and further discussion.

Results

Thirty-six patients were studied during the research, where four were excluded due to data collection failure. The main indications for TKA were 2 patients with rheumatoid arthritis, 16 with arthrosis and 13 with refractory pain (Figure 1). Thus, of the 32 participants, 25 patients presented deformity in genuvaro and 7 in genuvalgo.

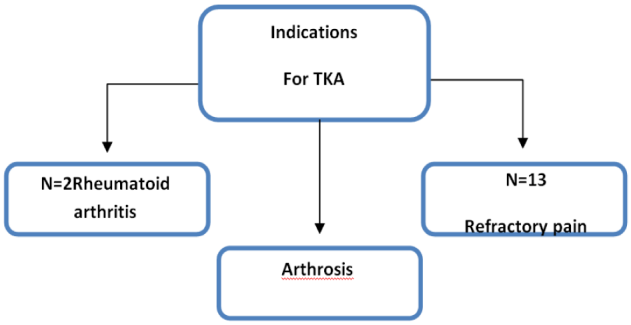

Figure 1: Indications for TKA.

The average age of the volunteers was 69 years ranging from 53 to 93 years, with a total of 22 female and 10 male patients. It should also be noted that 22 patients reported that they clearly understood the surgery, its possible detrimental effects on their health and postoperative pain.

As is well known by the medical profession, the process of knee degeneration due to arthrosis is mechanical, thus,

100% of the patients presented pain with the standard ambulation movement. Of these patients, 51% had reduced and / or limited knee extension and flexion movements, requiring even a wheelchair for locomotion.

In this context, the degree of limitation was so extensive that 16 patients (~ 50%) reported that they could not effectively perform even their personal hygiene activities, as an example.

The vast majority of patients who have undergone this surgical procedure have had pain for years, consequently abusing NSAIDs, common analgesics and even morphine-derived analgesics.

Regarding the undesirable effects of the drugs during the research, no cases of constipation, vomiting, attention disorder or mental confusion were found in any group. In the pregabalin group 1h before, cases of dizziness (n = 3), drowsiness (n = 2), insomnia (n = 1) and nausea (n = 1) were reported. None of these effects were found in the pregabalin group 24h before. In the placebo group there were reports of nausea (n = 1), dizziness (n = 5) and drowsiness (n = 2) (Figure 2).

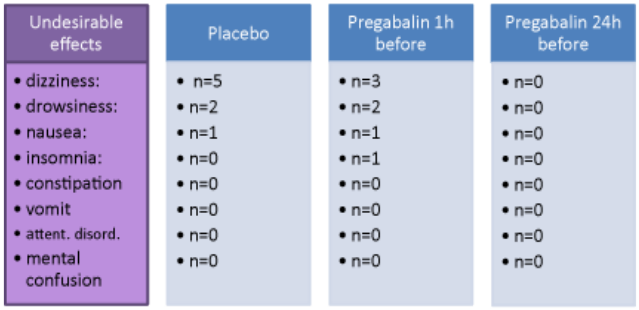

Figure 2: Undesirable effects.

During the research it was found that only 18.1% of patients had pathological knee pain less than 1 year and 81.8% reported pain for more than 3 years, some cases reaching even 20 years of pain.

Data on the Visual Analog Pain Scale (VAS) indicate that patients who did not take pregabalin before surgery, totaling 16 patients, reported an average VAS of 9.19. Concomitantly, patients taking pregabalin one hour before surgery (13 total) or 24 hours before surgery (4 total) reported mean VAS of 6.0 and 7.0, respectively, indicating a possible "immediate" analgesic action. "Of the drug.

Also regarding pain data, in all three groups analyzed, there was a reduction in the mean value reported for VAS (Table 1) when comparing pre- and postoperative 24 hours or 48 hours after the end of the surgical procedure. However, when applying a Student's t-test to compare such groups, statistical significance was observed in the VAS values of patients undergoing placebo treatment at postoperative evaluation 24h and 48h. In the pregabalin 1h before (P1B) and pregabalin 24 hours before (P24B) groups, statistical significance was observed in the 24h postoperative VAS assessments (Table 1).

Table 1: Mean value reported in VAS by patients undergoing TKA surgery.

Treatment group	VAS (average value)		
	Preoperativ	Postoperative 24h	postoperative 48h
Control	9,19*,†	6,06*,§	5,19†,§
Pregabalin 1h	6,50	4,83	4,17
Pregabalin 24h	7,00	3,25	3,24

* Significant difference, Student's t-test, p < 0,001
† Significant difference, Student's t-test, p < 0,001
§ Significant difference, Student's t-test, p < 0,001

These results indicate a possible partial blocking activity of the action of opioids administered postoperatively. Such antagonism can be explained by the action that pregabalin exerts by inhibiting the release of Serotonin and Noradrenaline, thereby preventing the indirect action of tramadol, which involves the inhibition of Noradrenaline and Serotonin reuptake which is essential for pain reduction.

Discussion

Evaluation of pain and quantity of opioids

Pregabalin is a structural analog compound of gamma aminobutyric acid (GABA) and acts on the central nervous system because it crosses the blood-brain barrier [19], due to this property its anticonvulsant, antihyperalgesic and anxiolytic actions. However, it binds with high affinity and specificity to voltage-dependent calcium channel alpha2-delta-1 proteins in the Central Nervous System, inhibiting their functional expression. This also inhibits calcium influx and the action of noradrenaline and serotonin neurotransmitters in the synaptic cleft [20]. These same neurotransmitters are part of the tramadol antinociception mechanism of action which, through two differents and independents but synergistic mechanisms of action, acts as an opioid agonist and indirectly performs

an action contrary to that of pregabalin, as it triggers mechanisms that inhibit the reuptake of noradrenaline and serotonin [21-28]. As this pharmacokinetics of pregabalin and tramadol have been studied in animals and in vitro separately, further studies are needed to elucidate such drug interaction.

However, this is the possible explanation for the fact that in our study similar effects of pain reduction were found between the groups receiving Placebo preoperatively and the pregabalin groups, both 1h before and 24h before surgery, as both used tramadol, as recommended by the Santa Casa Maceió antinociception guide.

In the pregabalin groups, both P1B and P24B at the time of surgery had a reduced VAS compared to the control group. It was observed that in the P1B group there was an immediate effect (1h after administration) and that lasted until the 24h postoperative reevaluation, however, there was no statistically significant reduction in the 48h postoperative period. As in the P24B group, pain reduction was statistically significant at the time of surgery (24h post-administration) and 24h postoperatively, and it was found that the antinociceptive effects of pregabalin did not last until the 48h postoperative reevaluation in any of the patients. group. Pharmacodynamicly this fact can be explained due to the fast absorption of pregabalin , reaching the maximum plasma concentration in about 1 hour and its half life being around 7 hours, thus explaining its ineffectiveness in post 48h of medication administration [29]. It is also observed that these characteristics did not change even when pregabalin is associated with tramadol [30].Effective pain reduction at the time of surgery (1h after administration) and 24h postoperatively when administering pregabalin (300mg) 1 hour before the procedure was also found by a Brazilian study conducted by Santiago et al. (2019) who, however, no significant reduction in inflammation mediating interleukin levels was found. Seeing that the immediate hypoalgesic effect (1 hour after administration) is present both when there are surgical procedures and false surgeries, thus observing the character of pregabalin for neuropathic pain reduction [31-38].

Corroborating our findings of hypoalgesia lasting up to 24 hours in both pregabalin groups even under a regime of implicit drug combinations of anesthetic procedures and after surgical trauma were also found by Zhang (2019), Sattari (2018), Park (2016) and Sawan (2014) [39-49]. However, in the study by Khetarpal [50] involving lower limb orthopedic surgeries, the pregabalin group (300mg) found effective hypoalgesia up to a maximum time of about 15h. The character of dose-dependent hypoalgesia becomes observable in a study using pregabalin 75mg to reduce postoperative septorhinoplasty pain in which the effectiveness remained until 6h after the procedure and did not persist in the 24-hour reassessment [51].

In this context, one should enthusiastically assess the fact that chronic post-thoracotomy pain does not persist with pregabalin for a prolonged period of 14 days, which gives patients a better quality of life [52]. However, further studies are needed to elucidate the correct long-term pregabalin prescription regimen for eliminating chronic postoperative pain.

However, in a study conducted in South Korea, a 75 mg dose of the drug (pregabalin) in tablet form was used one night before surgery and one capsule once a night until the 2nd postoperative day. In this study, there was no difference between the control group and the placebo group. Similar research was conducted with a total of 70 patients undergoing abdominal gastroplasty who randomly received oral pregabalin (75 mg) or an identical placebo 1 hour before surgery. Again, it was shown that there was no improvement in the quality of postoperative patient recovery and not even pain reduction. As the effectiveness of postoperative pain reduction has been demonstrated with dosages of 150mg and 300mg these interpretations become questionable.

Unwanted Effects

Undesirable effects in the 3 groups were not significant, a few patients on pregabalin or placebo experienced dizziness, drowsiness or nausea. However, none of the groups demonstrated sufficient effects to distinguish the causative drug in isolation, mainly because tramadol was used in all groups. A Korean study with healthy patients showed no increase in adverse effects when combining tramadol with pregabalin . Similar results with the use of pregabalin for postoperative pain reduction were found by Martins (2018), Zhang (2019), Mathiesen (2008) respectively after bariatric cholecystectomy and hip arthroplasty procedure.

In a postoperative TKA study following pregabalin use for another 3 months no patient had a common adverse effect of pregabalin even though the study addressed an extensive list of endocrine, cardiovascular, respiratory,

neurological, gastrointestinal, musculoskeletal, psychiatric disorders. and renal. The importance of assessing the amount of adverse effects in the control and pregabalin groups is even more necessary after studies in thoracic surgery relating the pregabalin groups to the reduction of adverse effects, especially headache, dysuria, constipation and nausea.

However, Park's [7] study found a significantly prevalent finding of blurred vision in the postoperative period after nasal surgery when using pregabalin before anesthesia.

Conclusion

Pregabalin has recognized side effects, but in the study it was observed safety in the administration of this drug in the patient group 24 hours before the surgical procedure compared to the patient group 1 hour before, as shown in Table 1.

There was a greater reduction in pain according to VAS in the postoperative period of 24 and 48 hours in the pregabalin group 24 hours before, compared to the others, as shown in table 1.

No decrease in postoperative opiod use was observed, as no study group achieved a VAS pain lower than 3 points over the length of stay.

Therefore, a larger study with larger patient samples and case controls is needed to obtain significant results.

References

1. Zabeu, Jose LuisAmim; MIGON, Eduardo Zaniol; JÚNIOR, Wilson Mello Alves. Pain following total knee arthroplasty - a systematic approach, Campinas. Rev Bras Ortop. V.45(5). p.384-39.2010.
2. Filos KS, Lehmann KA. Current concepts and practice in postoperative pain management: need for a change? EurSurg Res. 1999; 31:97-107.
3. Follin SL, Charland SL. Acute pain management: operative or medical procedures and trauma. Ann Pharmacother. 1997; 31:1068-76.
4. Maheshwari AV, Blum YC, Shekhar L, Ranawat AS, Ranawat CS. Multimodal pain management after total hip and knee arthroplasty at the RanawatOrthopedic Center. ClinOrthop Relat Res. 2009; 467:1418-23.
5. Sinatra RS, Torres J, Bustos AM. Pain management after major orthopedic surgery: current strategies and new concepts. J AmAcadOrthopSurg. 2002; 10:117-29.
6. Mangano DT, Wong MG, London MJ, Tubau JF, Rapp JA. Perioperative myocardial ischemia in patients undergoing noncardiac surgery--II: Incidence and severity during the 1st week after surgery. The Study of Perioperative Ischemia (SPI) Research Group. J Am CollCardiol. 1991; 17:851-7.
7. Park KK, Shin KS, Chang CB, Kim SJ, Kim TK. Functional disabilities and issues of concern in female Asian patients before TKA. Clin Orthop Relat Res. 2007; 461:143-52.
8. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. AnesthAnalg 97:534-540, 2003
9. Amin-Hanjani S, Corcoran J, Chatwani A: Cold therapy in the management of postoperative cesarean section pain. Am J ObstetGynecol 167:108-109, 1992
10. Antall GF, Kresevic D: The use of guided imagery to manage pain in an elderly orthopedic population. OrthopNurs 23:335-340, 2004
11. Aubrun F, Langeron O, Heitz D, Coriat P, Riou B: Randomised, placebo-controlled study of the postoperative analgesic effects of ketoprofen after spinal fusion surgery. ActaAnaesthesiolScand 44:934-939, 2000.
12. Ballantyne JC, Carr DB, de Ferranti S, Suarez T, Lau J, Chalmers TC, Angelillo IF, Mosteller F: The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. AnesthAnalg 86:598-612, 1998.
13. Abu-Shahwan I: Ketamine does not reduce postoperative morphine consumption after tonsillectomy in children. Clin J Pain 24:395-398, 2008.
14. Arnett RM, Jones JS, Horger EO: Effectiveness of 1% lidocaine dorsal penile nerve block in infant circumcision. Am J ObstetGynecol 163:1074-1080, 1990
15. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B: Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. Ann Intern Med 133:253-262, 2000.
16. Bamigboye AA, Hofmeyr GJ: Local anesthetic wound infiltration and abdominal nerves block during caesarean section for postoperative pain relief. Cochrane Database Syst Rev CD006954, 2009
17. Barber FA, McGuire DA, Click S: Continuous-flow cold therapy for outpatient anterior cruciate ligament reconstruction. Arthroscopy 14:130-135, 1998
18. Mathiesen O, Moiniche S, Dahl JB: Gabapentin and postoperative pain: A qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol 7:6,2007.
19. Kehlet H, Dahl JB: Anaesthesia, surgery, and challenges in postoperative recovery. *The Lancet* 2003, 362:1921-28.
20. Butler GS, Hurley CAM, Buchanan KL, Smith-VanHorne J: Prehospital education: Effectiveness with total hip replacement surgery patients. Patient EducCouns 29:189-197, 1996.
21. Freedman BM, O'Hara E: Pregabalin has opioid-sparing effects following augmentation mammoplasty. AesthetSurg J 28:421-424, 2008.
22. Gonano C, Latzke D, Sabeti-Aschraf M, Kettner SC, Chiari A, Gustorff B: The anxiolytic effect of pregabalin in outpatients undergoing minor orthopedic surgery. J Psychopharmacol 25:249-253, 2011.
23. Ittichaikulthol W, Virankabutra T, Kunopart M, KhamhomW, Putarawuthichai P, Rungphet S: Effects of pregabalin on post-operative morphine consumption after abdominal hysterectomy with/without salphingooophorectomy: A randomized, double-blind trial. J Med Assoc Thai 92:1318-1323, 2009.
24. Jokela R, Ahonen J, Tallgren M, Haanpaa M, Korttila K: Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 100:834-840, 2008.

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25. Chizh BA, Gohring M, Troster A, Quartey GK, Schmelz M, Koppert W. Effects of oral pregabalin and aprepitant on pain and central sensitization in the electrical hyperalgesia model in human volunteers. Br J Anaesth 2007; 98:246–254.

26. Ifuku M, Iseki M, Hidaka I, Morita Y, Komatus S, Inada E. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. Pain Med 2011; 12:1112–1116.

27. Katz J, Clarke H, Seltzer Z. Preventive analgesia: quo vadimus? AnesthAnalg 2011; 113:1242–1253.

28. Macrae W, Davies H. Chronic post surgical pain. In: Crombie IK, Linton S, Croft P, Von Knorff M, LeResche L, editors. *Epidemiology of pain*. Washington, DC: IASP Press; 1999. 125–142.

29. Parvataneni HK, Ranawat AS, Ranawat CS. The use of local periarticular injections in the management of postoperative pain after total hip and knee replacement: a multimodal approach. Instr Course Lect. 2007; 56: 125-31.

30. SINGLA, Neil et al. Pregabalin for the treatment of postoperative pain: results from three controlled trials using differen surgical models. Journal of pain Research. Pasadena, p. 9-20. 23 dez. 2

31. YIK, Jing Hui et al. Perioperative pregabalin does not reduce opioid requirements in total knee arthroplasty. **Knee Surgery, Sports Traumatology, Arthroscopy**, p. 1-7, 201.

32. MARTINS, Marcelo J. et al. Pregabalin to improve postoperative recovery in bariatric surgery: a parallel, randomized, double-blinded, placebo-controlled study. **Journal of pain research**, v. 11, p. 2407, 2018.

33. LEE, Cheol et al. Pregabalin and Dexmedetomidine Combined for Pain After Total Knee Arthroplasty or Total Hip Arthroplasty Performed Under Spinal Anesthesia. **Orthopedics**, 2018.

34. YIK, Jing Hui et al. Perioperative pregabalin does not reduce opioid requirements in total knee arthroplasty. **Knee Surgery, Sports Traumatology, Arthroscopy**, p. 1-7, 2019.

35. DAVIES, Anthony et al. Functional biology of the α2δ subunits of voltage-gated calcium channels. **Trends in pharmacological sciences**, v. 28, n. 5, p. 220-228, 2007.

36. FIELD, Mark J.; OLES, Ryszard J.; SINGH, Lakhbir. Pregabalin may represent a novel class of anxiolytic agents with a broad spectrum of activity. British journal of pharmacology, v. 132, n. 1, p. 1-4, 2001.

37. GAJRAJ, N. Pregabalin: its pharmacology and use in pain management. Anesthesia & Analgesia Journal, Texas, USA, v. 105, p. 1805–1815, 2007.

38. DRIESSEN, B.; REIMANN, W.; GIERTZ, H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. British journal of pharmacology, v. 108, n. 3, p. 806-811, 1993.

39. DAYER, Pierre; COLLART, Laurence; DESMEULES, Jules. The pharmacology of tramadol. **Drugs**, v. 47, n. 1, p. 3-7, 1994.

40. BOCKBRADER, H. et al. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. Clinical Pharmacokinetics, Michigan, USA, v. 49, p. 661–669, 2010.

41. ZHANG, Dan; YOU, Guangqiang; YAO, Xiaoxiao. Influence of pregabalin on post-operative pain after laparoscopic cholecystectomy: A meta-analysis of randomized controlled trials. Journal of Minimal Acess Surgery, 2019.

42. MARTINS, Marcelo J. et al. Pregabalin to improve postoperative recovery in bariatric surgery: a parallel, randomized, double-blinded, placebo-controlled study. Journal of pain research, v. 11, p. 2407, 2018.

43. LEE, Soyoung et al. A pharmacokinetic drug-drug interaction study between pregabalin and tramadol in healthy volunteers. European journal of clinical pharmacology, v. 74, n. 12, p. 1605-1613, 2018.

44. LI, Shuangjiang et al. Does pregabalin effectively and safely relieve postoperative pain in patients undergoing pulmonary resections?. Interactive cardiovascular and thoracic surgery, 2019.

45. BOCKBRADER, Howard N. et al. Clinical pharmacokinetics of pregabalin in healthy volunteers. The Journal of Clinical Pharmacology, v. 50, n. 8, p. 941-950, 2010.

46. RODRIGUES, Rafaela Figueiredo et al. Influência da duloxetina e amitriptilina na farmacocinética e efeito biológico da pregabalina para tratamento da dor crônica em animais. 2016.

47. POURFAKHR, Pejman et al. Low-dose preoperative pregabalin improves postoperative pain management in septorhinoplasty surgery: a double-blind randomized clinical trial. European Archives of Oto-Rhino-Laryngology, p. 1-7, 2019.

48. SATTARI, Hossein et al. Preoperative oral pregabalin reduces acute pain after thoracotomy. Open access Macedonian journal of medical sciences, v. 6, n. 9, p. 1606, 2018.

49. SAWAN, Hind et al. Pregabalin reduces opioid consumption and improves outcome in chronic pain patients undergoing total knee arthroplasty. The Physician and sportsmedicine, 2014.

50. KHETARPAL, Ranjana et al. Gabapentin vs pregabalin as a premedication in lower limb orthopaedics surgery under combined spinal epidural technique. Anesthesia, essays and researches, v. 10, n. 2, p. 262, 2016.

51. POURFAKHR, Pejman et al. Low-dose preoperative pregabalin improves postoperative pain management in septorhinoplasty surgery: a double-blind randomized clinical trial. European Archives of Oto-Rhino-Laryngology, p. 1-7, 2019.

52. ANWAR, Sibtain et al. Prolonged Perioperative Use of Pregabalin and Ketamine to Prevent Persistent Pain after Cardiac Surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists, 2019.