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GABAPENTIN FOR ACUTE POSTOPERATIVE PAIN

Evidence Based Medicine Guideline

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SUMMARY
Gabapentin (Neurontin™) has gained significant interest as part of a multi-modal pain management strategy for the control of acute pain. There has been considerable variation in both the dose and the regimen used in recent clinical trials. Most have relied on pre-operative dosing and have utilized a single dose of 300 to 1200 mg. Higher doses seem to show a decrease in postoperative pain, a reduction in opioid requirement, and reduction in opioid related adverse effects such as nausea, vomiting, and ileus, with a propensity for causing sedation and dizziness.

RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **A single pre-operative dose of gabapentin 300 – 600 mg may be considered to reduce post-operative opioid consumption**
    - **Patients age ≥ 65 years should be limited to a preoperative dose of ≤ 300 mg**
  - **Avoid pre-operative gabapentin doses >600 mg due to increased risk of side effects**
- **Level 3**
  - **Scheduled gabapentin doses should be avoided in the post-operative period unless otherwise indicated for neuropathic pain**
  - **Initial gabapentin doses for post-operative neuropathic pain should be limited to 300 mg per 24 hours**
  - **Wean gabapentin over at least 2 weeks if receiving high doses (≥ 900 mg per 24 hours) for at least 4 weeks**
  - **High dose gabapentin taper may be considered for patients with concomitant post-operative pain and alcohol withdrawal to decrease benzodiazepine use (see Alcohol Withdrawal Guideline)**
  - **Patients on gabapentin prior to admission should be resumed on gabapentin, if clinically appropriate**

INTRODUCTION

Gabapentin and other anticonvulsant medications have been established as an effective treatment for chronic neuropathic pain and are commonly used for such conditions as herpetic neuralgia, diabetic neuropathy, and phantom limb pain following amputation. These medications act by reducing the activity of calcium channels in GABA-ergic neurons thereby activating the noradrenergic spinal pathway which in turn reduce the expression of the spinal cord excitatory amino acids glutamate and aspartate. There has been interest in this medication for use as an adjunct for acute pain as part of a multi-modal pain management strategy.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

LITERATURE REVIEW

In 2004, Pandey et al. investigated the use of a single 300 mg dose of gabapentin preoperatively in patients undergoing single level lumbar discectomy (1). They found that patients had a decrease in use of post-operative fentanyl (233.5±141.9 µg vs. 359.6±104.1 µg). In a follow up study in 2005, they evaluated gabapentin in increasing dosages to evaluate for the optimal pre-operative dose (2). Patients were divided into 5 groups and received placebo, 300 mg, 600 mg, 900 mg, or 1200 mg. They found that pre-operative gabapentin decreased patient use of fentanyl at all dosages. There was no advantage found in raising the dose from 600 mg to 1200 mg. They concluded 600 mg was the optimal dose for pre-operative gabapentin administration.

In 2006, Ho et al. performed a review of 16 randomized controlled trials (RCTs) evaluating the use of preoperative gabapentin in controlling postoperative pain (3). This was a very heterogeneous group that included orthopedic, gynecologic, urologic, breast, and head/neck surgeries. They found that a single preoperative dose of 1200 mg effectively reduced postoperative pain and opioid consumption. Multiple doses of gabapentin preoperatively, and continued postoperatively, did not appear to reduce pain scores. Incidence of opioid adverse effects such as vomiting, and pruritus were lower in the gabapentin group. Although not statistically significant, there was a trend toward a lower incidence of nausea, urinary retention, and constipation in the gabapentin group. The incidence of sedation was higher in the gabapentin group and there was a trend towards increased dizziness.

In 2007, Peng et al. published a meta-analysis of RCTs in the management of acute postoperative pain using gabapentin (4). This analysis included 1181 patients including open gynecologic procedures, orthopedic procedures of the spine and lower extremity, breast surgery, procedures of the head and neck, open nephrectomy, and laparoscopic cholecystectomy. Most studies used doses of 600 mg to 1200 mg preoperatively in addition to continued administration in the postoperative period. A study of laparoscopic cholecystectomy included in the analysis used a dose of 300 mg. They found that gabapentin resulted in a 35% reduction in total analgesic consumption in the first 24 hours following surgery. Gabapentin also resulted in 27% to 39% reduction in visual analog scale (VAS) pain scores in the first 24 hours postoperatively. It reduced opioid-related nausea, vomiting, and pruritus although there was an increase in dizziness and sedation. They did note that there was significant heterogeneity in the magnitude of the benefit from adding gabapentin. Subgroup analysis based on surgical procedure, gabapentin dosing, or study quality could not explain the heterogeneity observed.

Solak et al. in 2007 evaluated gabapentin in patients with chronic post-thoracotomy pain (5). This group compared gabapentin in stepwise increasing dosages of up to 2400 mg daily with naproxen. The gabapentin was increased in a stepwise fashion during the period of treatment until the patients were all on 2400 mg daily by the end of the study period. Patients in the naproxen group received 1000 mg daily in divided doses. At the conclusion of the 60 day trial, patients in the gabapentin group showed improved VAS pain scores and improved Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scores compared to patients in the naproxen group. In 2006, Sihoe et al. evaluated gabapentin in the treatment of chronic pain after chest surgery (6). This was a heterogeneous group of patients. Twelve patients were chest trauma victims, 22 with video assisted thoracoscopic surgery (VATS) approach, 8 with open thoracotomies, and 3 with median sternotomies. Patients were started on a dose of gabapentin 300 mg daily and titrated up to a total dose of 900 mg daily for uncontrolled symptoms. At the conclusion of the study, 73% of patients reported a reduction in their pain score, and 42% reported a reduction of 50% or more.

In 2010, the Cochrane Library published a review of four RCTs evaluating single-dose gabapentin in doses from 250 to 500 mg in treating acute pain (7). Three studies used a third molar dental extraction model, and one in major orthopedic surgery. All patients were given gabapentin in combination with opioids, or NSAIDs. This review found that there was a significant decrease in the amount of opioids used, and less requirement for rescue medication in the gabapentin group. They noted the number needed to treat (NNT) for a 50% pain reduction was 11. They noted that this dose of gabapentin was inferior to other analgesics such as ibuprofen 400mg, naproxen 50 mg, or acetaminophen 1000 mg. The authors of this review question whether a dose response can be demonstrated and whether the combination of gabapentin with other analgesics gives better pain relief than either alone.

Gabapentin has also been evaluated as part of a multi-modal pain management regimen. In 2013, Paul et al. included gabapentin in a regimen including morphine, ketorolac, and acetaminophen (8). They used a dose of 600 mg orally preoperatively followed by 200 mg every 8 hours during the postoperative period. They assessed morphine requirements and VAS pain scores both at rest and during movement over the first 72 hours following surgery. They found that the addition of gabapentin did not result in a significant decrease in morphine requirement nor did it affect the VAS pain score. Gabapentin as part of a multi-modal pain regimen was also evaluated by Monks et al. in women receiving cesarean delivery. In this study, gabapentin was added to a regimen which

included spinal anesthesia as well as postoperative opioids (9). Patients received a dose of 600 mg orally preoperatively and 200mg every 8 hours in the postoperative period. They found a statistically significant, but small decrease of 7 mg of morphine consumption in the gabapentin group, but an increase in sedation. There was also a statistically significant, but small decrease in the VAS pain score. There were no statistically significant differences at 48 hours. The authors concluded that gabapentin is of questionable benefit when given as part of a multi-modal pain regimen after cesarean delivery.

In 2016, Mayo Clinic published a retrospective chart review of patients undergoing major laparoscopic surgery lasting > 90 minutes. There was a statistically significant increased risk of respiratory depression associated with the use of gabapentin (OR 1.47; p <0.001) (10).

In 2020, the Canadian Perioperative Anesthesia Clinical Trials Group performed a meta-analysis of randomized controlled trials to determine the efficacy and risks of perioperative use of gabapentinoids including gabapentin and pregabalin. They included 281 trials resulting in a pooled group of 24683 participants. They converted pain scaling to a 100-point scale and determined a reduction in pain of 10 to be clinically significant. At the 6hr, 12hr, 24hr, 48hr, and 72hr time points, there was a pain reduction on the 100-point scale of less than 10 for each time point suggesting a minimal improvement in pain reduction. There was no significant difference in post operative chronic pain in the gabapentinoid groups. There was a reduction in required opioid requirement in the 72 hours after surgery. There was a moderate increased risk of ataxia, falls, and visual disturbance in the gabapentinoid group as well as a low increased risk of delirium, respiratory depression, and dizziness. With minimal reduction in pain and an increased risk of adverse events, gabapentinoids should be used cautiously in perioperative period (11).

In 2021, a study from the University of North Carolina was published in the Anesthesia and Analgesia Journal looking at gabapentinoid and prolonged opioid use in patients over 65 years old. This was a retrospective cohort study of nearly 14000 patients of which 21% were given preoperative gabapentinoids. They did not demonstrate a reduced risk of prolonged opioid use identified as requiring an outpatient opioid prescription. They did not demonstrate a statistically significant difference between the group that received pre-operative gabapentinoids and the group that did not (12).

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