QUARTER 1, 2024 | VOLUME 12 | NUMBER 1

BLUE CROSS Medical Bulletin

BC Division of Blue Cross Laboratories Pvt Ltd.

ANALGESIC EFFECT OF DEXTROMETHORPHAN FOR POST-OPERATIVE PAIN MANAGEMENT

Pain management is a critical component of postsurgical care, as it influences patient safety and outcomes, and inadequate control has been associated with the development of chronic pain syndromes. Traditional pharmacological management of postoperative pain with opioids have side effects, of which the most serious are respiratory and cardiovascular depression associated with excessive sedation and also dependence.

The search for alternative pain control strategies has focused on the N-methyl-D-aspartate (NMDA) receptors and their antagonists which were recently shown to alleviate somatic and neuropathic pain sensations in both animal and human models.

Dextromethorphan, an NMDA receptor antagonist, most routinely used as an oral antitussive, stands out among well-studied and emerging pharmacological adjuncts for postoperative pain due its robust safety profile and unique pharmacology. Its clinical applicability is supported by its wide therapeutic window, lack of major contraindications, and the fact that there are no special monitoring requirements for its use.

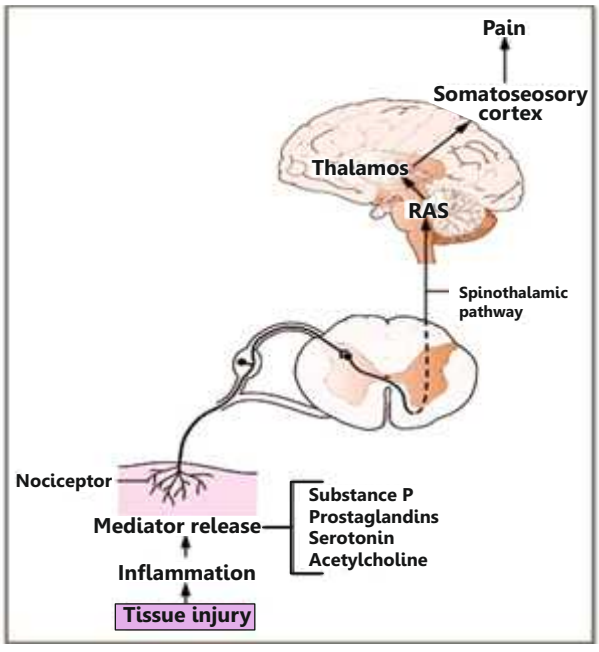
With respect to its unique pharmacology, Dextromethorphan is structurally related to alkaloid opioids such as morphine, but does not interact with the mu (μ) receptor or produce typical opioid effects, including dependence. It is also known to have many interactions with several different receptor sites, including activity as a low affinity, non-competitive antagonist at NMDA receptors.

➡ The potential of Dextromethorphan in pain control

I. Mechanism

After tissue injury, pain is transmitted via A-δ and C-sensory fibers to dorsal horn neurons, leading to hyper excitability via activation of NMDA receptors. The resulting effect causes both peripheral sensitization, which is a reduction in the threshold of nociceptive afferents, and central sensitization, which is an activity-dependent increase in the excitability of spinal neurons. This process is known as the "wind-up" phenomenon, which produces prolonged and more severe pain.

Dextromethorphan is thought to mitigate these effects by blocking NMDA receptors along the spinothalamic tract, reducing the threshold for pain transmission via the A-δ and C-sensory fibers. However, it is also likely that additional pathways are involved. Recent preclinical studies have shown dextromethorphan mediated improvements in hyperalgesia due to the inhibition of glucocorticoid receptor-mediated neuroinfammation.



II. Clinical Evidence

There is strong evidence that Dextromethorphan has beneficial effects when used to treat pain in human subjects. Numerous randomized controlled trials have shown that dextromethorphan leads to reduced postoperative pain and opioid consumption.

- A 2016 meta-analysis investigating perioperative dextromethorphan as an adjunct for postoperative pain identified 40 studies. Of which, in 848 patients from 14 trials, opioid consumption favoured Dextromethorphan. In 950 patients from 13 trials, pain at 4-6 hours favoured dextromethorphan. In 797 patients from 12 trials, pain at 24 hours favoured dextromethorphan. This suggests Dextromethorphan use perioperatively reduces postoperative opioid consumption at 24-48 hours and pain.
- The study of Kawamata et al. showed that a single Dextromethorphan premedication of 30 or 45 mg administered 60 min before tonsillectomy under general anaesthesia was effective in reducing post-tonsillectomy pain sensation, even upon swallowing, in adult patients. This single dose also reduced the pain score and diclofenac requirement for 7 days following surgery.
- Henderson et al. also confirmed the efficacy of oral Dextromethorphan during the first two postoperative days in patients premedicated with 40 mg the night before and three times/day for 48 hours after hysterectomy and with very few side effects.
- Another recent clinical study for evaluation of oral 60 mg Dextromethorphan for treatment of postoperative pain is underway which will further support the aforementioned result.

Thus, all the above indicate a beneficial role of Dextromethorphan as part of multi-modal analgesic therapy, for postoperative pain control. For these patients, oral Dextromethorphan at doses of 30–90 mg appears to have an advantage over other antagonists in reducing the sensation of pain and sparing the requirement of conjointly administered analgesics, and has proven to have no or a low rate of untoward side effects.

Source: Jones et al. Trials.2023; 24:238, King MR, et al. Anesthesiology. 2016; 124(3): 696–705, Avi A, et al. Can J Anesth. 2000; 47(6): 585–596

POTENTIAL BENEFICIAL EFFECTS OF TENEBLU (DIPEPTIDYL PEPTIDASE-4 INHIBITORS) ON BONE HEALTH IN TYPE 2 DIABETICS

Type 2 diabetes mellitus (T2DM), a prevalent chronic condition has affected 422 million individuals worldwide, exhibiting significant global health challenges. It is often associated with comorbidities like cardiovascular disease, kidney, diseases etc.

Osteoporosis and reduced bone mineral density (BMD) frequently coexists with T2DM. Studies have shown that patients with T2DM have a higher risk of fractures & moreover, chronic hyperglycemia, a hallmark of T2DM, may adversely affect bone metabolism through increased bone resorption and decreased bone formation, leading to lower BMD thus posing a significant health burden.

Dipeptidyl peptidase-4 inhibitors (DPP-4i), extensively used in the management of T2DM offer several benefits, including a low risk of hypoglycemia, neutral effects on weight, and a good safety profile. Some studies have suggested their beneficial effect on bone metabolism.

Potential Mechanism: The positive effects of DPP-4i on BMD and osteoporosis risk might be explained by several possible mechanisms;

- In bone biology, DPP-4i have been shown to improve bone formation markers, suggesting a possible role in promoting osteoblast activity.
- DPP-4i have been found to increase the levels of glucagon-like peptide-1 (GLP-1), which is involved in influencing bone metabolism. GLP1 can directly act on osteoblasts, promoting their proliferation and differentiation, therefore enhancing bone formation.
- Some studies have also proposed an indirect mechanism where the glucose-lowering effects of DPP-4i might lead to improved bone health by preventing the deleterious effects of hyperglycemia on bone remodelling (increased bone resorption and decreased bone formation).

Clinical evidence: Recently a meta-analysis comprising of 10 studies with a combined population of 2,14,541 patients evaluated the impact of DPP-4i on bone health among patients with T2DM, which reflected the above possible mechanism in their findings. First, the usage of DPP-4i enhanced BMD in a statistically meaningful way, indicating that they might have a beneficial effect on BMD in people with T2DM, a population that is more likely to have bone loss. Second, a significantly reduced risk of osteoporosis was associated with DPP-4i indicating that DPP-4i protects type 2 diabetics from developing osteoporosis.

This above findings was found in alignment with a previous meta-analysis (28 trials, 21,055 patients) conducted on a similar objective where DPP-4i was reported to have a decreased risk of fractures among T2DM patients.

Therefore, DPP-4i's positive influence on bone health in T2DM patients indicates a benefit of this antihyperglycemic medication that goes beyond its well-known effects on glycemic management and that it may contribute to a more comprehensive approach to managing such patient group, addressing both their glycemic and bone health needs.

Source: Huang L, et al. J Clin Densitom. 2024; 27(1): 101455, Trakarnvanich T, et al. J Diabetes Res. 2021.

PROPHYLACTIC MEFTAL-P (MEFENAMIC ACID) AS ANALGESIC FOR CHILDREN RECEIVING VACCINATION

The most important and economical preventive measure against a variety of pediatric diseases is vaccination. However, one of the main causes of low vaccine adherence and immunization coverage is needle pain during routine vaccinations.

The World Health Organization (WHO) has highlighted the need for initiatives to address needle pain during vaccination in order to promote effective immunization practices worldwide.

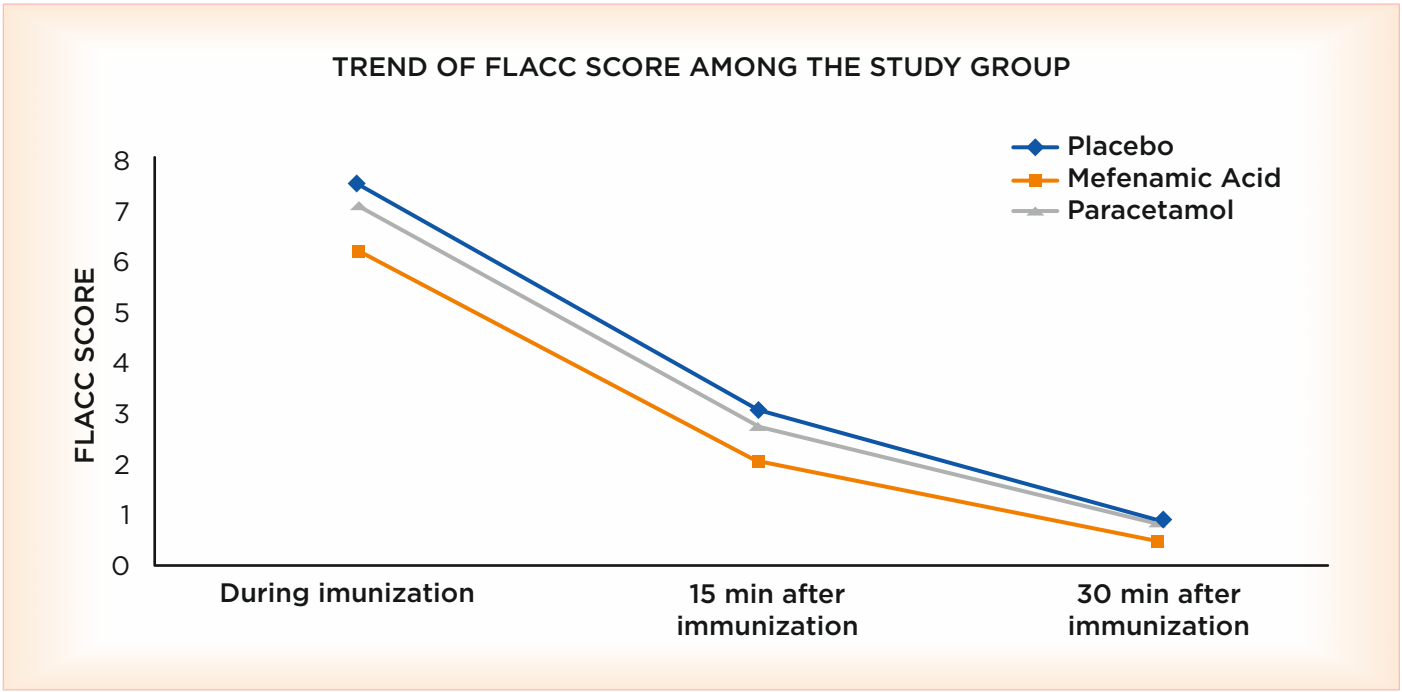
Various analgesics have been studied to reduce needle pain associated with vaccination, like EMLA cream (Eutectic mixture of local anesthetics), paracetamol, or ibuprofen, but lack of evidence has limited its use.

A cochrane review suggested Mefenamic acid use as an acute analgesic in adults after surgical procedures. Post-surgery use of Mefenamic acid has been shown in numerous studies to be an effective single dose for managing acute pain following orthopedic surgeries, dental procedures, and episiotomies.

Mefenamic acid is also a widely used and effective drug in pediatrics for the treatment of fever and pain.

Fever is the most commonly reported adverse event following vaccination and antipyretic medicines are prescribed by healthcare workers for the treatment of fever as well as for prophylaxis. Most of the analgesics for needle pain are prescribed after the administration of vaccination. It is not clear if prophylactic analgesics can alleviate needle pain during vaccination, therefore this important issue was addressed in a recent study where efficacy of oral Mefenamic acid (4mg/kg/dose) and paracetamol (10mg/kg/dose) over placebo as a prophylactic analgesic during vaccination was studied. Both the drugs (45 children in each group; 6 weeks to 7 years of age) were administered orally 30 minutes before vaccination.

There was a significant difference in FLACC (Face, Leg, Activity, Cry, and Consolability) scores at the time of administration (p =0.010) and at 15 minutes (p = 0.014) with Mefenamic acid compared to placebo, while with Paracetamol no statistically significant local analgesic effect was found at any point of vaccine administration. In fact, one study that compared the analgesic effect of paracetamol or Mefenamic acid on the intensity of headaches due to migraine in adults, found that Mefenamic acid is more potent than paracetamol as analgesic. This finding corroborated with the above study where Mefenamic acid was more effective as an analgesic whereas paracetamol had an equivocal effect as compared to placebo respectively.



Mefenamic acid, has both peripheral and central action whereas paracetamol has central rather than peripheral action. The mechanism of preventive analgesia is due to the inhibition of the central or peripheral sensitization of nociceptors before their stimulation, thus attenuating its excitability further.

Hence, prophylactic, single-dose Mefenamic acid is potent, more effective and should be considered in reducing needle pain due to vaccination in children to deal with vaccine hesitancy and to improve vaccine coverage.

Source: Pasi R, et.al. Ther Adv Vaccines Immunother; 2023; 11.

Dr. Prabhu Kasture (MD, DPH)
Dy. Director Medical Services & Pharmacovigilance
PHONE NO.: 022-666638043
EMAIL: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013