

Dosing of dexamethasone in chronic cancer pain

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Editorial

Pain is the distressing and feared symptom experienced by cancer patients and has a negative impact on the quality of life. The prevalence of chronic pain is around 30-50% in cancer patients undergoing active treatment for solid tumours and 70-90% in patients with advanced disease.¹ Cancer pain management is therefore an essential and integral part of patient care and requires multimodal therapy as it involves complex neuro-physiological mechanisms of pain which include inflammation, compression and ischemia. Multimodal therapy, which includes primary analgesics and adjuvants (co-analgesics) helps in better pain relief and minimises the side effects. Adjuvants play an important role in multimodal therapy of which corticosteroids are the most commonly used. According to World Health Organization (WHO), adjuvants are to be considered at each step of WHO ladder.²

Corticosteroids for chronic pain

Corticosteroids are a versatile group of drugs widely being used in cancer for a range of indications. They are used in conditions with proven evidence of their role like metastatic spinal cord compression,³ superior vena caval syndrome, raised intracranial pressure, bowel obstruction as well in those conditions lacking definitive role of steroids like chronic cancer pain, nausea, fatigue, and anorexia. They are also used to prevent immediate pain flare up following radiotherapy in vertebral metastases.⁴ In relation to chronic cancer pain, it is being used in bony pain, visceral pain due to obstruction of hollow viscus, organ capsule distension, neuropathic pain due to infiltration or compression of neural structures and metastatic spinal cord compression. The possible role of steroids in every step of nociception: transduction, transmission, modulation and pain perception has been raised though the exact mechanism of action remains unclear. The mechanisms suggested include-inhibition of collagenase expression (key enzyme involved in tissue destruction during inflammation), reduction of pro-inflammatory cytokines

and stimulation of lipotropin synthesis (inhibition of eicosanoid production). Hence steroids are most effective in inflammatory pain. They also inhibit spontaneous discharges from injured nerve and modulate neuroimmune interactions thereby decreasing neuropathic pain.

However, corticosteroids are often “double edged swords”; though they provide rapid symptomatic relief they also have side effects that are dose and time dependent. Hence, clear guidelines regarding the “when, what, how, how much and how long” of steroid therapy must be established. Among the steroids, dexamethasone has been used more frequently because of its low mineralocorticoid activity, longer half-life, higher potency, availability of oral and parenteral formulations, higher glucocorticoid activity, 7 times more anti-inflammatory effect than prednisone and affordability. Numerous groups have assessed the utility of dexamethasone in cancer pain using a wide range of doses without arriving at conclusive objective evidence regarding its efficacy (Table 1).

Table 1 A Summary of studies evaluating dexamethasone dosing in cancer pain management

Authors	Study details	Dexamethasone Dosing	Adverse effects	Results	Conclusion
Hanks GW et al. ⁵	373	4 -16 mg/day. 4 mg daily (n=7) 8 mg (n=4) 16 mg (n=2). Maintenance-0.5 mg on alternate days to 4 mg twice a day	Dexamethasone -more likely than prednisolone to cause oro-pharyngeal candidosis, psychological disturbance and hyperactivity but less edema, weight gain, and dyspepsia.	8/13 responders for dexamethasone, 8/21 responders for prednisone	Dexamethasone has better effect in cases of nerve compression as compared to prednisone.
Hardy JR et al. ⁶	Uncontrolled 106(total)	8mg (4-16mg)	Most common side-effects that were most probably attributable to steroid therapy were oral candidosis and proximal myopathy	81% better pain score at 2 weeks 84% better pain score at 3 weeks	If used according to guidelines benefits outweigh risks. Short term is beneficial.

Table Continued...

Authors	Study details	Dexamethasone Dosing	Adverse effects	Results	Conclusion
Bruera E et al. ⁷	Double blind, parallel arm trial. 51 included; 43 completed. Primary outcome-intensity of nausea. Secondary outcome-pain intensity, fatigue and appetite loss.	Intervention: 20mg dexamethasone /day + metoclopramide 60 mg/day. Control: placebo+ metoclopramide 60 mg/d. Duration- 7days.	Ankle edema, restlessness, insomnia	Pain, vomiting, well-being, and quality of life remained unchanged in both groups at both times.	Dexamethasone was not superior to placebo in the management of chronic nausea in patients with advanced cancer. Pain intensity at baseline low in both arms. Authors therefore query meaning fullness of pain as outcome measure.
Mercadante SL et al. ⁸	RCT 76 advanced cancer patients	2 groups: O-received conventional opioid therapy, OS- conventional opioid therapy + 8 mg dexamethasone		Corticosteroids did not provide significant added analgesia to opioids but decreased opioid related GI symptoms in patients with limited survival and improved sense of well-being.	Further studies with larger sample size needed to detect any minimal differences in analgesia between 2 groups.
Yennurajalingam S et al. ⁹	120 participants; 2 groups. Fatigue was the primary outcome measured.	Intervention group: 4 mg dexamethasone orally twice a day for 14 days. Control group: placebo orally twice a day for 14 days	The frequency of adverse effects was not significantly different between the 2 groups.	Pain as measured by ESAS (Edmonton symptom assessment scale) significantly better on dexamethasone on day 8 but not on day 15. Mean (standard deviation) improvement in the FACIT-F subscale at day 15 was significantly higher in the dexamethasone than in the placebo group.	Dexamethasone is more effective than placebo in improving CRF (cancer related fatigue) and quality of life in patients with advanced cancer.
Denton A et al. ¹⁰	Retrospective analysis 1179 patients reviewed-768 patients received at least 1 course of steroids. Commonly -non-specific indications-40.4%, neurological (25.3%).	Non-specific indications-1-8mg (dose range), Capsular stretching-(4-12mg).	Not able to draw useful conclusions		Corticosteroids are widely being used in palliative care settings mostly for non-specific indications.

Dosing of Dexamethasone

Dexamethasone has been used in various dose ranges in chronic cancer pain patients despite paucity of randomised controlled trials and weak evidence of its efficacy. Although there are some studies which report benefit of steroids in pain control their validity is limited because of small sample size. A recent meta-analysis by Hawood et al.¹¹ was done to evaluate the efficacy of corticosteroids in treating cancer related pain in adults.¹¹ Fifteen studies that met the inclusion criteria were identified but only 6 studies were included in meta-analysis study for pain intensity as insufficient data was available for other studies. The studies which assessed dexamethasone described a dose range of 8mg to 20mg orally mostly as twice daily dosing. Also there is lack of an appropriate parenteral dose for dexamethasone. The results concluded that the evidence of efficacy of dexamethasone was weak albeit they might relieve cancer pain for short period and further adequately powered randomised trials are needed to evaluate the efficacy and to recommend duration of therapy and ideal dosing. It is left to the discretion of the attending physician to assess the benefit carefully, treat for shortest possible time and discontinue if no adequate

relief is observed. Further research is required to conclusively find the optimal dose and dosing schedule of dexamethasone for cancer pain management as adjuvant.

Conflicts of Interest

The authors do not have any Conflict of interests.

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