

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Oncologic emergencies**

MEDICINE REVIEW

1. Executive Summary

Date: November 2019
Medicine (INN): Dexamethasone IV/oral
Medicine (ATC): H02AB02
Indication (ICD10 code): Metastatic spinal cord compression (MSCC) (G95.2)
Patient population: Cancer patients with spinal cord compression due to tumour metastasis
Prevalence of condition: Local prevalence data not available; 40% of patients with cancer estimated to develop metastatic spinal disease and 10-20% of these patients will develop symptoms of MSCCⁱ. Incidence of MSCC likely to increase as cancer survival rates improveⁱⁱ
Level of Care: Secondary level – Adult hospital
Prescriber Level: Doctor
Current standard of Care: n/a
Efficacy estimates: (preferably NNT) Greenberg et al, **1980** (n=80)ⁱⁱⁱ
Dexamethasone vs placebo:
Efficacy: 57% of patients ambulatory (28% were non-ambulatory before treatment onset); Pain relief.
Safety: Nonfatal ruptured duodenal ulcer on day 4 of treatment in one patient
Motivator/reviewer name(s): Ms TD Leong, Dr A Sherriff
PTC affiliation: Dr A Sherriff - Free State PTC

2. Name of author(s)/motivator(s)

Ms TD Leong, Dr A Sherriff

3. Author affiliation and conflict of interest details

- *Ms TD Leong:* National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee (2017-2020); No conflicts of interest declared.
- *Dr A Sherriff:* HOD Oncology: University of the Free State, Adult Hospital Level Committee (2017-2020); No applicable conflicts of interest.

4. Introduction/ Background

Spinal cord compression develops in cancer patients due to epidural tumour metastasis^{iv}. There are three mechanisms for epidural MSCC.

1. Bone metastases may expand into the epidural space, compressing the cord.
2. Destruction of vertebral cortical bone creating instability that leads to vertebral body collapse and displacement of bony fragments into the epidural space.
3. A paraspinal mass can cause neuroforaminal extension into the epidural space.

Symptoms associated with spinal tumours are caused by the disruption of spinal cord tracts, nerve roots, and cerebrospinal fluid flow pathways. The symptoms are dependent on the location of the tumour, but the most common presenting symptom is nocturnal back pain. Other common symptoms include lower extremity weakness, sensory loss, and altered bowel and bladder function^v.

Patients may be either ambulatory or paraplegic at the time of diagnosis^{vi}.

MSCC causes significant morbidity and disability in large numbers of patients across a spectrum of cancers. However, there is limited evidence to guide clinicians and patients in choosing appropriate treatments^{vii}.

Radiotherapy with initial administration of corticosteroids or decompressive surgery are standard treatment regimens for MSCC. Dexamethasone is the corticosteroid of choice.

Corticosteroids use may cause hyperglycemia, peripheral edema, infections, proximal myopathy and gastritis (incidence of these adverse effects correlates with dose and frequency)^{viii ix}.

5. Purpose/Objective i.e. PICO

-P Adults with a malignancy presenting with spinal cord compression

-I Dexamethasone IV/oral

-C Placebo

-O Prevention of further neurological decline, preservation of spinal stability

6. Methods:

a. Data sources: PubMed, Cochrane

b. Search strategy

i. *Cochrane Library*: (Metastatic spinal cord compression) AND (corticosteroids), restricted to Cochrane review.

- 4 reviews retrieved, 3 excluded as not relevant to PICO question, 1 synthesised (see table below).

ii. *Pubmed*: (("secondary"[Subheading] OR "secondary"[All Fields] OR "metastatic"[All Fields]) AND ("spinal cord compression"[MeSH Terms] OR ("spinal"[All Fields] AND "cord"[All Fields] AND "compression"[All Fields]) OR "spinal cord compression"[All Fields])) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields]) AND RCTs[All Fields] AND "humans"[MeSH Terms]

- 3 publications retrieved, 2 excluded, 1 relevant publication retrieved (the same Cochrane review that was retrieved in the Cochrane Library).

c. Excluded studies:

Author, date	Type of study	Reason for exclusion
George et al, 2008 ^x	Cochrane review	Updated 2015 version published
Lohre et al, 2012 ^{xi}	Systematic review	Not relevant to PICO question (fractionation radiation schedules).
Lee et al, 2015 ^{xii}	Cochrane review	Not relevant to PICO question (positioning and spinal bracing for pain relief).
Martinez-Zapata et al, 2006 ^{xiii}	Cochrane review	Not relevant to PICO question (calcitonin for metastatic bone pain).
Haywood et al, 2019 ^{xiv}	Cochrane Review	Not relevant to PICO question (cancer-related dyspnea).

d. Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
George et al, 2015 ^x	Cochrane review	7 RCTs evaluating radiotherapy, surgery and corticosteroids in Metastatic extradural spinal cord compression (MESCC). 3 small RCTs evaluated corticosteroid therapy.	Adults with clinical or radiological evidence of extradural spinal cord compression or cauda equina compression caused by metastatic cancer. (Primary tumours of the spinal cord was excluded).	High-dose corticosteroids (> 32mg/day) vs moderate-dose (<32mg/day) or no corticosteroids, with/ without surgery/radiotherapy	<u>Primary outcome:</u> • Ambulation <u>Secondary outcome:</u> • Survival • Pain relief • Urinary incontinence • Local recurrence • Adverse effects • Quality of life • Participant & caregiver satisfaction	High-dose steroids vs moderate-dose /no corticosteroids: <u>Primary outcome:</u> • Enhancing ambulation: 60% vs 55%; RR 1.08, 95% CI 0.81 to 1.45; 3 RCTs, n=105 – <i>ns</i> (low quality evidence) <u>Secondary outcome:</u> • Survival over two years: 11% vs 10%; RR 1.11, 95% CI 0.24 to 5.05; 1 RCT, n= 57 - <i>ns</i> (low quality evidence) • Pain reduction (78% versus 91%; RR 0.86, 95% CI 0.62 to 1.20; 1 RCT, n=25 – <i>ns</i> (low quality evidence) • Urinary continence (63% vs 53%; RR 1.18, 95% CI 0.66 to 2.13; 1 RCT, n= 34 - <i>ns</i> (low quality evidence) • Serious adverse effects: 17% vs 0%; RR 8.02, 95% CI 1.03 to 62.37; 2 RCTs, n=77– <i>ns</i> (moderate quality evidence). None of the RCTs reported satisfaction with care or quality of life in participants.	Limited RCT evidence of low quality suggests that high dose steroids may not offer any beneficial effects vs moderate doses in enhancing ambulation, long-term survival, reducing pain, improving urinary incontinence. The uncertainty of the optimal dose of steroids with/without surgery/radiation warrants more high quality RCT research, and the authors reported that some trials were in progress. Limited evidence of moderate quality shows that high doses of corticosteroids have a high risk of adverse effects, such as perforated gastric ulcer, psychoses and deaths due to infection. The authors of the review conclude that, “Early detection; and treatment based on neurological status, age and estimated survival, are crucial with all treatment modalities” ^{xv}

ns = not statistically significant

e. Evidence quality:

7. Alternative agents: n/a

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS						
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>							
BENEFITS & HARM	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	If moderate dose of steroids is used						
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group: n/a</p> <p>List specific exclusion from the group: n/a</p>	<p>Rationale for therapeutic alternatives included: n/a</p> <p>References: n/a</p> <p>Rationale for exclusion from the group: n/a</p> <p>References: n/a</p>						
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	Experts working in the Oncology environment can attest to the clinical impact of the use of corticosteroids prior to surgery or radiation						
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th><th>Cost (ZAR)</th></tr> </thead> <tbody> <tr> <td></td><td></td></tr> <tr> <td></td><td></td></tr> </tbody> </table> <p>Additional resources: n/a</p>	Medicine	Cost (ZAR)				
Medicine	Cost (ZAR)							
EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p>							
FEASIBILITY	<p>Is the implementation of this recommendation feasible?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>							

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Recommendation

Based on this evidence review, the Adult Hospital Level Committee recommends moderate dose corticosteroids to reduce inflammation, oedema and pain in metastatic spinal cord compression; either with/without surgery or radiation. NICE^{xvi} and Canadian guidelines^{xvii} recommend starting with doses of 16 mg per day.

Rationale: Limited evidence of low quality suggests that moderate dose corticosteroids may be beneficial in enhancing ambulation, long-term survival, reducing pain, improving urinary incontinence ; but there is uncertainty regarding the optimal dose. However, high doses of steroids are associated with a higher risk of adverse effects (such as perforated gastric ulcer, psychoses and deaths due to infection).

Level of Evidence: III Systematic review of low quality RCTs

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Monitoring and evaluation considerations: n/a

Research priorities: Adequately powered, multicentre RCTs are needed to determine the optimal dosage and duration of corticosteroids. Patients should also be optimally selected for their suitability for radiotherapy or decompressive surgical interventions as the primary treatment modalities.

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