

THE TABLET: PALLIATIVE CARE PHARMACY TIPS



October 14, 2022

Vol. 2, No. 17

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TODAY'S TOPIC: Steroids and Wound Healing

Background:

Steroids are commonly used in the palliative care setting for comfort given that glucocorticoid receptors are widely expressed throughout tissues of the body. Activation of these receptors causes a variety of effects. Steroids have been used for nausea, fatigue, bone pain, inflammation, and bowel obstruction (not all-inclusive). Because of their wide mechanism, they can also come with a host of potential side effects such as hyperglycemia, increased infection risk, insomnia, fluid retention, GI ulceration, and impaired wound healing. Impaired wound healing is a main concern, especially in our post-operative population. The impaired wound healing is thought to be due to steroids' interference with inflammation, fibroblast proliferation, collagen turnover, wound contraction and re-epithelialization but ultimately is not completely understood. Weighing risk versus benefit entails weighing expected benefit timeline to potential side effect profile timeline, and patient prognosis.

Importance:

Steroids are used often in the palliative care setting. It is important for palliative care clinicians to be aware of the potential timeline for side effect presentation of commonly used medications to weigh risk versus benefit prior to use in our population.

The Literature:

[Am J Surg. 2013;206\(3\):410-417.](#)

Corticosteroids and wound healing: clinical considerations in the perioperative period

Objective: Review the three aspects of the effects of corticosteroids on wound healing

Methods: Literature review from 1949-2011, included both animal studies and human studies

Outcomes: Wound tensile strength, effect of chronicity of steroids on wound healing, and effect of timing of steroids on wound healing

Results:

- Wound tensile strength
 - o Animal studies (n = 16)
 - Difficult to compare these studies given differences in methodology and outcome measurements
 - ~30% reduction in wound tensile strength at cortisone doses of 15-40mg/kg/day (approximately equivalent to 200-560mg/day of prednisone or 30-85mg/day of dexamethasone in a 70kg person)
 - Difficult to extrapolate to humans as wound tensile strength is likely different across species
 - o Human studies (n = 13)
 - Wound healing impaired for those who received corticosteroids; duration and dose varied across studies
- Effect of chronicity of steroid use on wound healing

Study (Ref)	N	Equivalent dose (mg/day of prednisone)	Duration	Wound complication rate (control %)
Numerous Diseases				
Green, 1965 ⁵¹	38	10.8 ± 7	1 day-13 mo	29 (NR)
Engquist et al, 1974 ⁶⁰	100	18 pts: <10 74 pts: >10	19 pts: <1 yr 73 pts: >1 yr	44 (22)
Reding et al, 1990 ⁶²	55	51 (15-480)	18 mo	13 (2)
Rheumatoid Arthritis				
Popert & Davis, 1958 ⁶⁸	15	12.4 ± 3	25 ± 16 mo	20
Garner et al, 1973 ⁶⁵	100	2.5-15	Variable	71 (25)
Escalante & Beardmore, 1995 ⁶⁶	204	6.4 ± 2.2	NR	15.9
Jain et al, 2002 ⁶⁷	30	8.8 (4.25-20)	NR	3.3 (9.5)
Inflammatory Bowel Disease				
Price, 1968 ⁷⁴	80	NR	NR	15 (40)
Knudsen et al, 1976 ⁷²	41	>40	NR; >2 mo	66 (27)
Allsop & Lee, 1978 ⁶⁹	162	>20	NR	31
Post et al, 1991 ⁷³	265	NR	NR; preoperative	19 (7)*
Ziv et al, 1996 ⁷⁵	361	169 pts: >20 192 pts: <20	NR; >1 mo	8 (6) 12 (6)
Bruewer et al, 2003 ⁷⁰	219	73 pts: >20 146 pts: <20	NR	18 (11) 12 (11)

N is the number of patients or the number of operations from each study in the experimental group. Dose is adjusted for equivalent doses of prednisone (1 = 1 mg/day prednisone). Duration refers to the number of months that patients took corticosteroids preoperatively. Wound complication rate is defined as disruption, persistent drainage, dehiscence, infection, or wound failure. In cases where no control group was included, there are no parenthetical numbers provided. *Indicates there was a statistically significant difference in complication rates between the experimental and control groups.
NR = not reported; pts = patients.

- Effect of timing of steroid administration on wound healing
 - o Animal studies
 - If administered 3 days or more after wounding, corticosteroids have no effect on wound tensile strength
 - Limited clinical studies, none mentioned in this article

Conclusion: More research needs done

[J Int Med Res. 2006 Mar-Apr;34\(2\):223-30.](#)

Abdominal wound dehiscence in patients receiving long-term steroid treatment

Objective: The aim of this study was to determine whether the pre-operative dose and post-operative total dose of steroids influence abdominal wound dehiscence

Methods: Cohort study, patients on long-term steroids prior to laparotomy

- Post-operative wound healing assessed daily during rounds

Results:

- n=28 patients receiving long-term (>3 months) steroids prior to surgery

	AWD (n = 7)	NAWD (n = 21)	P-value
Age (years)	54.3 ± 12.3	47.0 ± 16.0	NS
Pre-operative total dose of steroid (mg)	39 755 ± 54 298.4	19 130.2 ± 21 810	NS
Duration of steroid administration (months)	124.3 ± 103.0	101.1 ± 115.9	NS
Steroid dose within pre-operative 30 days (mg)	625.7 ± 383.6	645.7 ± 588.3	NS
Post-operative dose of steroid (mg)	404.3 ± 147.1	135.6 ± 118.7	< 0.001
Duration of wound healing (days)	57.3 ± 18.0	12.4 ± 3.8	< 0.001
Wound infection	5	7	NS

AWD = abdominal wound dehiscence; NAWD = non-abdominal wound dehiscence (no dehiscence); total steroid doses in prednisone equivalents

- The post-operative doses of steroids and the duration of wound healing showed significant differences between AWD and NAWD (P < 0.001)

Conclusion: Abdominal wound dehiscence may be influenced by the post-operative rather than the pre-operative steroid dose

CLINICAL PEARL: Although impaired wound healing is a well-known adverse effect to steroid use, little is known about how this would affect clinical practice in palliative care

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[Chochrane Database Syst Rev. 2018 Nov 23;11\(11\):CD011940.](#)

Adverse side effects of dexamethasone in surgical patients

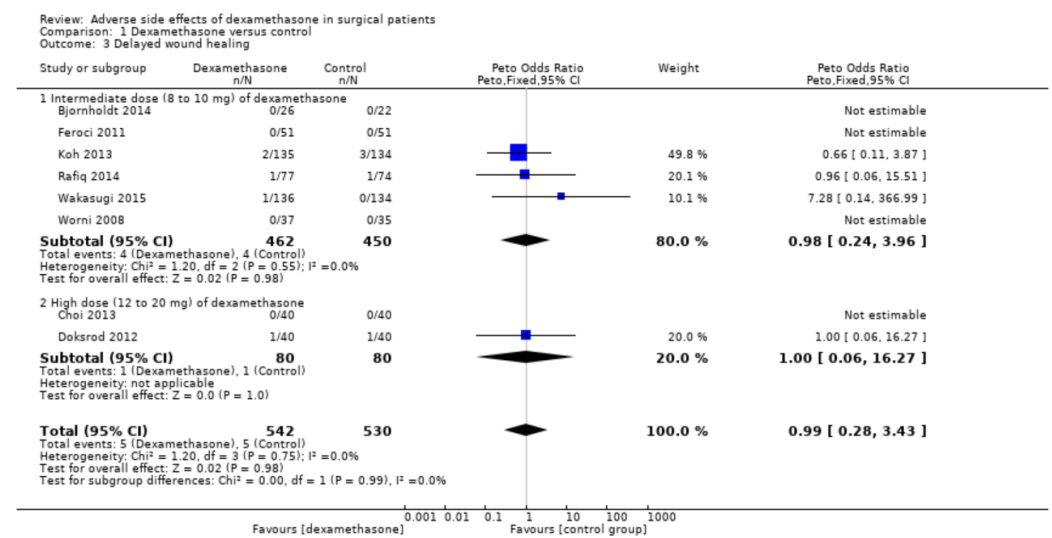
Objective: To assess the effects of a steroid load of dexamethasone on postoperative systemic or wound infection, **delayed wound healing**, and blood glucose change in adult surgical patients

Methods: Meta-analysis of RCTs of adults who received **single dexamethasone dose** (4mg-20mg) **prior** to surgery

- Proportion of wounds that had not healed within 30 days
- Subgroup analysis for with and without diabetes and doses

Results:

- 9 studies assessed delayed wound healing (n=1072); one excluded in the meta-analysis as scoring system for wound healing used and not comparable
- Effects of dexamethasone on delayed wound healing are unclear because the wide confidence interval includes both meaningful benefit and harm (Peto OR 0.99, 95% CI 0.28 to 3.43; 1072 participants, eight studies; $I^2 = 0\%$; low-quality evidence).



Comparison 1 Dexamethasone versus control, Outcome 3 Delayed wound healing.

- Subgroup analysis
 - o No differences between different dosages of dexamethasone
 - 8 to 10 mg dexamethasone: Peto OR 0.98, 95% CI 0.24 to 3.96; 912 participants, six studies; $I^2 = 0\%$
 - 12 to 20 mg dexamethasone: Peto OR 1.0, 95% CI 0.06 to 16.21; 160 participants, two studies; $I^2 =$ not applicable
- Incidence of delayed wound healing of 0-2%
- Participants at increased risk for delayed wound healing (diabetes or those on immunosuppressant medications) were not included in the RCTs in this meta-analysis

Conclusion: It is uncertain whether dexamethasone has an effect on delayed wound healing in the general surgical population owing to imprecision in trial results

Bottom Line:

- Although impaired wound healing is a well-known adverse effect to steroid use, little is known about how this would affect clinical practice in palliative care...
- It is possible that post-operative dosing of steroids may pose a higher risk for impaired wound healing than pre-operative dosing of steroids
- Single doses of dexamethasone prior to surgery did not have significant impact on wound healing. Differences between moderate or high doses did not exist
- More research needs done to compare timing, doses, and duration of steroid use, surgery, and wound healing as available evidence is inconclusive to help guide the clinical practice of utilizing steroids in the peri-operative period for symptom management needs