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實 EVIDENCE 証

Hospital Authority Head Office
Professional Services & Medical Development Division

Clinical Effectiveness Unit
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Short course high-dose steroid therapy and avascular necrosis of bone (AVN)

Introduction

Up to 90% of severe acute respiratory syndrome (SARS) patients in Hong Kong had received steroid during hospitalization. Among survivors ≥ 18 years of age, an average cumulative dose equivalent to 16.1 ± 13.7 gm of hydrocortisone was given over a period of 20.2 ± 10.9 days. Avascular necrosis (AVN) of bone is a known hazard of pharmacological use of steroid but we have little data to inform us of its prevalence following a short course of high dose steroid. Reports of AVN, some of which affected unusual or multiple locations began to appear in patients after 3 to 4 months of recovery from SARS.

Although the EBM approach is not a good method for studying adverse event, 2 systematic reviews were performed in September & October to help decide the value of mass MRI screening in this group of patient. Because a screening program is only beneficial if treatment available given at an earlier stage could improve the likelihood of favorable outcomes compared to treatment given when the disease would make its presence known in the usual course of events, we started by examining evidence on core decompression, the most widely practiced procedure for AVN of femoral head. The result was published in the HA HTA Report Series "HTA 03/11 - Core Decompression for Avascular Necrosis of the Femoral Head" accessible in the HA intra- & inter-net. We then searched the literature for reported prevalence of AVN following short courses of high dose steroid particularly in doses comparable to our SARS cohort. We report the latter findings in this issue of EVIDENCE.

We searched for English citations in the MEDLINE, EMBASE, CINAHL and COCHRANE Library for the period 1970 to October 2003 using MeSH headings "Osteonecrosis", "Avascular Necrosis", "Femoral Head Necrosis", "Adrenal Cortex Hormones/ae, de, to [Adverse Effects, Drug Effects, Toxicity]", "Glucocorticoids/ ad, ae, to [Administration & Dosage, Adverse Effects, Toxicity]" and key words "short term", "short course", supplemented by manual review of bibliographies in retrieved articles.

Quantitative Review

Level 2 evidence: 1 quantitative review (poor quality) and 2 cohort studies with control (poor quality) on AVN following short or long-term steroid exposure.

<table>
<tr><th>Citation</th><th>Study design</th><th>Observation</th></tr>
<tr><td>1</td><td>Study design: Systemic review. MEDLINE search (1970-1985) supplemented by selected bibliographies in retrieved articles. Included 15 case-control studies, 5 observational studies, 2 RCTs.
Statistical method: Data was pooled and association was calculated by regression analysis.
Limitations:
♦ Quality of Primary
♦ Search limited to English & French citations
♦ Did not address study quality assessment, number of reviewers involved, or suitability in combining data for meta-analysis.
♦ 11 of 15 case-control studies found no significant difference in steroid dose between cases and controls</td><td>Reported AVN ranged from 0-31%.
Multiple regression analyses showed that cumulative oral steroid dose was a powerful predictor of AVN ($p < 0.01$).
Bolus steroid given less than once per month was not associated with AVN risk.
Plots of cumulated AVN incidences vs. steroid dose (pool data) shows correlation ($r = 0.61$-0.80) between daily total dose & AVN rate: a 4-6% absolute risk increase per 40 mg HCE/day rise in oral steroid.</td></tr>
<tr><td>2</td><td>Study period: 1978-1988
Subjects: Patient with asthma or inflammatory arthritis
Design: Prospective case-control study.
Continuous, intermittent or burst steroid (n = 151) vs. Control (n = 49)
Outcome measures: Harris hip score, XR finding
FU: 10 years (1420 hip-years)
Limitations:
♦ Small sample size and high dropout rate.
<table>
<tr><th></th><th>Control</th><th>Steroid (asthma)</th><th>Steroid (arthritis)</th><th>Total</th></tr>
<tr><td>Recruited</td><td>49</td><td>73</td><td>78</td><td>200</td></tr>
<tr><td>Analyzed</td><td>20</td><td>32</td><td>39</td><td>91</td></tr>
</table>
♦ Patients received intermittent & burst steroid had much lower doses. Their numbers were not provided.</td><td>Average steroid dose per mode of administration (analyzed cohort)
<table>
<tr><th rowspan="2">Steroid</th><th colspan="2">Average dose (gm HCE)</th></tr>
<tr><th>Asthma</th><th>Arthritis</th></tr>
<tr><td>Continuous</td><td>8.0</td><td>7.7</td></tr>
<tr><td>Intermittent</td><td>0.2</td><td>0.032</td></tr>
<tr><td>Burst</td><td>0.5</td><td>0.09</td></tr>
</table>
Outcome: no change in Harris Hip Score and no AVN detected in both groups.</td></tr>
<tr><td>3</td><td>Study period: 1989-1996
Subject: Patient with acute spinal cord injury
Design: Prospective study. Steroid coverage 141mg/kg HCE over 24 hours (n = 59) vs. Historical control without steroid (n = 32)
Outcome measure: MRI of humeral & femoral heads
FU: 6-12 months
Limitations:
♦ Small sample size.
♦ Historical control.
♦ Inadequate information on comparability.
♦ Short follow-up.</td><td>No AVN in either groups</td></tr>
</table>

FU = Follow up; HCE = Hydrocortisone equivalent; MRI = Magnetic Resonance Imaging

1. Felson DT, Anderson JJ. Across-study evaluation of association between steroid dose and bolus steroids and avascular necrosis of bone. Lancet 1987 Apr 18:1(8538): 902-5.
2. Colwell CW Jr., Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics 1996 Nov;19(11): 941-6.
3. Wing PC, Nance P, Connel DG, Gagnon F. Risk of avascular necrosis following short term megadose methylprednisolone treatment. Spinal Cord 1998;36(9): 633-36.

Level 3 evidence: 8 prospective or retrospective observational studies on AVN following short or medium-term steroid exposure. Poor quality.

Citation	Study design	Observation
4	Study period: 1985-1989 Subject: Patient underwent orthognathic surgery, usual steroid dose 7.3g HCE given over 30 hours Study design: Retrospective review by matching records for a concurrent 54 months period: orthognathic surgery (n = 1276) & total hip replacement (n = 1497) Limitation: • Matching patient records could not ensure adequate FU of all orthognathic patients • Hip replacement is surrogate indicator of late AVN. It does not identify early AVN femoral head or AVN at other locations.	No patient in the hip replacement group had previous orthognathic surgery.
5	Study period: 1977-1979 Subject: 66 patients underwent neurosurgery for intracranial aneurysm & received mean cumulative dose 6.6gm HCE within 17 days Study design: Retrospective case series Outcome measure: Patient to report joint pain & history of AVN. FU: Mean 50.3 months. Limitation: • No formal medical / radiological assessment. • High dropout rate.	Outcome: 11 died, 11 lost, 13 had joint pain, 1 had bilateral AVN required total hip replacement, 30 reported asymptomatic.
6	Study period: 1963-1971; 1971-1976 Subject: Renal allograft transplant recipients Study design: Retrospective case series. • 1963-1971: 242 recipients received oral maintenance steroid (1-1.3mg HCE/kg) for 3-8 months • 1971-1976: 146 recipients received IV pulse (1 gm methylprednisolone on day of surgery & for acute graft rejection) + oral maintenance steroid for 9-12 months FU: 9 to 12 months Limitation: • Not prospective study. • No standard FU plan to ensure detection of all AVN. • Short FU	AVN reported in 5% of recipients transplanted during 1963-1971 & 4.8% of recipients transplanted during 1971-1976.
7	Study period: 1966-1981 Subject: 546 renal transplant recipients, graft survival > 12 mths Study design: Retrospective case series + case-control study (n = 29 each) Outcome measure: joint pain, limitation in movement (XR if symptomatic) & XR hip for all patients in 1982/1983 FU: 12-134 months Limitation: • Cohort received a wide range of steroid dose (30-60 gm HCE). • Wide range of FU duration.	29 patients developed AVN in 39 hips between 6-134 months (mean 16) after transplant. No significant difference in cumulative steroid doses between AVN patients & controls (age, sex, graft survival matched).
8	Steroid period: 1966-1981 Subject: 50 BMT recipients with survival > 2 yrs, received steroid for GVHD. Study design: Retrospective case series Outcome measure: FU: ≥2 years Limitations: • No data on steroid administration pattern & cumulative dose &received by the cohort. • Haemic malignancy, aplastic anemia & conditioning by total body irradiation are confounding variables. • No standard FU plan to ensure detection of all AVN.	5 patients developed AVN within 2 years of BMT. Onset ranging from 249-731 days. Lowest steroid dose involved in AVN patients was 56mg/kg.

9	Study period: Not reported Subject: 28 children with nephrotic syndrome or nephritis received cumulative steroid dose of 8-256 gm HCE Study design: Retrospective case series Outcome measure: XR screening (hips, knees, upper & lower thirds of the femoral shaft & upper third of tibial shaft) FU: 1-16 (mean 8) years after steroid Rx Limitations: ♦ Abstract / brief report provided scanty information. ♦ Small sample size. ♦ Marked variation in steroid dose & FU period.	No AVN detected
10	Study period: 1984-1988 Subject: 212 SLE patients, average dose & duration = 170 mg HCE/day for 95 days (ave. cumulative dose 16.2 gm HCE) Study design: Prospective case series Outcome measure: XR & bone scan FU: 5 years Limitations: ♦ High dropout rate (only 62 patients completed study). ♦ SLE is a confounding variable.	9 of 62 patients completed study had developed AVN.
11	Study period: Started 1978-1979 Subject: 42 renal transplant recipients (32 were adults), average steroid dose at one year = 56 mg HCE/day. Study design: Prospective case series Outcome measure: Whole body bone scan every 6 months FU: 2-3 years Limitation: ♦ Small sample size. ♦ Brief information on steroid dose	7 patients (16.7%) had AVN

4. Precious D, Armstrong J, Morrison A, Field C. The incidence of Total Hip Replacement in Orthognathic Surgery Patients Receiving Short-Term Steroid Therapy. J Oral Maxillofac Surg 1992 Sep; 50(9):956-957.
5. Sambrook PN, Hassall JE, York JR. Osteonecrosis after high dosage, short-term corticosteroid therapy. J Rheumatol 1984 Aug; 11(4): 514-6.
6. Susan LP, Braun WE, Banowsky LH, Straffon RA, Bergfeld JA. Avascular necrosis following renal transplantation. Urology 1978 Mar;11(3):225-9.
7. Haajanen J, Saarinen O, Laasonen L, Kuhlback B, Edgren J, Slatis P. Steroid treatment and aseptic necrosis of the femoral head in renal transplant recipients. Transplant Proc 1984 Oct;16(5):1316-9.
8. Atkinson K, Cohen M, Biggs J. Avascular necrosis of the femoral head secondary to corticosteroid therapy for graft-versus-hot disease after marrow transplantation: effective therapy with hip arthroplasty. Bone Marrow Transplantation 1987 Dec; 2(4):421-6.
9. Gregg PJ, Barsoum MK, Soppitt D, Jackson RH. Avascular necrosis of bone in children receiving high-dose steroid treatment. Br Med J 1980 Jul:281(6233):116.
10. Ono K, Tohjima T, Komazawa T. Risk factors of avascular necrosis of the femoral head in patients with systemic lupus erythematosus under high-dose corticosteroid therapy. Clin Orthop Relat Res 1992 Apr;277:89-97.
11. Spencer JD, Maisey M. A prospective scintigraphic study of avascular necrosis of bone in renal transplant patients. Clin Orthop Relat Res 1985 Apr;194:125-35.

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實 EVIDENCE 証 in CONTEXT

Hospital Authority Head Office *Clinical Effectiveness Unit*

Professional Services & Medical Development Division *Addendum to '實 EVIDENCE 証' Issue 19, 2003*

AVN Screening in Post-SARS Follow-up

There is little good evidence on the prevalence of AVN following a short course of high dose steroid. 11 studies included in this review fall within level 2⁻ and 3 categories of the SIGN classification (http://www.sign.ac.uk/) and practically all have considerable methodological flaws that limit their applicability. These studies reported a wide ranging prevalence of AVN (0 to 31%) following use of short and medium-term high dose steroid.

It is important to note that the EBM approach is not a good method for studying adverse event (AE), as (i) most studies are designed to address efficacy more than AE; (ii) sample size and duration of follow up are often inadequate to identify uncommon AE; (iii) reports of AE often cannot prove causal relationship as AE may be affected by the underlying disease and other circumstantial factors; and (iv) publication bias favors over and under reporting of AE. Interpretation should be made in light of these general limitations and also of the specific inadequacy identified in individual studies, which we tried to summarize in the evidence tables. Furthermore, differences in study design, subject characteristics, nature of underlying disease, wide range of steroid dosage and duration of treatment, outcome measures and length of follow-up, etc. will all limit the generalizability of their findings to our SARS cohort.

After much discussion in the HA SARS Collaborative Group (HASCOG), it was agreed to coordinate mass MRI screening for AVN in SARS survivors at around 6-9 months post-discharge. This would help to clarify the risk of AVN following SARS and following high dose steroid given over a discrete period of time, as well as in monitoring AVN progress in this group of patients to enable better planning of treatment strategy.

Additional information and comments relative to this issue are welcome, and should be addressed either to 實 EVIDENCE FORUMS 証, available from <http://ekg> or Dr SP Lim at splim@ha.org.hk.