Meta-Analysis

The effect of corticosteroids on the prevention of fat embolism syndrome after long bone fracture of the lower limbs: a systematic review and meta-analysis*

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Abstract

Objective: To analyze the available evidence regarding the effect that corticosteroids have on the prevention of fat embolism syndrome after long bone fracture of the lower limbs or pelvic fracture. **Methods:** In March of 2007, we performed a search of various electronic databases, including Medline, the *Excerpta Medica* database, the Cochrane Library, the Latin American and Caribbean Health Sciences Literature database and the Scientific Electronic Library Online. We selected randomized controlled trials that compared the effect of corticosteroids with that of placebo (or standard care) on the prevention of fat embolism syndrome after long bone fracture of the lower limbs or pelvic fracture. References from the studies included were also reviewed. **Results:** Six studies were included. The pooled relative risk for developing fat embolism syndrome was 0.16 (95% CI: 0.08-0.35) in the corticosteroid group as compared with the control group. The pooled relative risk for developing hypoxemia was 0.34 (95% CI: 0.19-0.59) in the corticosteroid group as compared with the control group. **Conclusion:** The analysis of evidence showed that corticosteroids decrease the risk of developing fat embolism syndrome and hypoxemia after long bone fracture of the lower limbs.

Keywords: Embolism, Fat; Adrenal Cortex Hormones; Meta-Analysis.

* Study carried out at Jackson Memorial Hospital, Miami, FL, USA, and at the *Universidade Federal de Santa Catarina* – UFSC, Federal University of Santa Catarina – Florianópolis, Brazil.

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Introduction

Fat embolism refers to the presence of fat globules in the pulmonary parenchyma and in the peripheral circulation in general after trauma. However, fat embolism syndrome (FES) denotes a combination of signs and symptoms that classically include petechiae, respiratory distress, and mental confusion.[1-4] In 90% of the cases, FES occurs 24 to 48 h after contusion trauma complicated by long bone (diaphyseal) fracture, although it is also associated with various other conditions such as arthroplasty, acute hepatic necrosis, *delirium tremens*, liposuction, pancreatitis, and sickle cell anemia.[5-9]

Although the treatment for FES is principally clinical support, some specific measures are important for its prevention: correction of shock in patients who suffered trauma; adequate preoperative rehydration[10]; early surgical fixation of diaphyseal fractures[11-13]; and, more recently, modified surgical techniques designed to decrease intramedullary pressure in the treatment of femoral fracture.[14-19]

Of the various medications tested and used in the prevention of FES, corticosteroids have been the most studied and have been shown to have beneficial effects. However, the findings have been inconsistent. Some studies have shown that corticosteroids decrease the incidence of FES after diaphyseal fracture,[20-22] whereas others, including the most recent clinical trial, have found that there is statistically significant decrease.[23,24] The studies were small, and the lack of statistical significance might be related to the size of the sample. Therefore, we decided to carry out a systematic review involving a meta-analysis of the clinical trials in order to clarify the role of corticosteroids in the prevention of FES. The objective of this study was to determine whether the use of corticosteroids decreases the risk of FES in patients who have suffered diaphyseal fracture of the lower limbs or pelvic fracture.

Methods

We included studies that met the following criteria:

- design: randomized, controlled clinical trial;
- population: patients who suffered fracture of the lower limbs or pelvic fracture;
- intervention: administration of corticosteroids in the intervention group versus placebo (or standard care) in the control group; and
- outcome: development of FES.

The diagnosis of FES was established based on at least one of the following findings: petechiae; respiratory failure/hypoxemia; and mental confusion. The secondary outcome was hypoxemia, although the evaluation of hypoxemia in the clinical trial was not considered a requirement for the inclusion of the study in this systematic review.

In March of 2007, we searched Medline, the *Excerpta Medica* database, the Cochrane Library, the Latin American and Caribbean Health Sciences Literature (LILACS) database, and the Scientific Electronic Library Online (SciELO).

We conducted the following searches with no language restriction:

In Medline (date range, 1966-2007)

1) Full text terms: fat embolism syndrome AND corticosteroids.
2) Text term limited to clinical trials: fat embolism.

In the *Excerpta Medica*

3) Full text terms: fat embolism AND corticosteroids.

In the Cochrane Library

4) Full text term: fat embolism.

In the LILACS database (consists of texts in Portuguese and Spanish)

5) Full text term: *embolia gordurosa* (fat embolism).

In the SciELO database (consists of texts in Portuguese and Spanish)

6) Full text term: *embolia gordurosa* (fat embolism).

We reviewed the available abstracts and reference lists in order to identify potentially relevant studies. We also carried out a manual search for references cited in the requested articles and studies published in the annals of conferences.

We determined whether there was allocation concealment, which prevents the patients and the recruiting participants from having prior knowledge of the allocation of groups in randomized, controlled clinical trials. According to the Cochrane Collaboration Handbook,[25] the allocation concealment was classified as adequate, unclear, inadequate, or not used.

We used a structured chart to collect the relevant data. Data used in the statistical analysis were transferred to the Stata Intercooled program, version 9.2.

The data were pooled, and we performed a meta-analysis using a fixed effect model. The outcomes were binary. Relative risks and 95% confidence intervals were obtained using the Mantel-Haenszel[26] method. We calculated the number of patients who need to be treated in order to prevent an event. After analysis, tests of heterogeneity and publication bias were carried out, and a value of $p < 0.05$ was considered indicative of heterogeneity or publication bias.

Results

Systematic review/Study characteristics

The numbers of articles obtained through the respective searches were as follows: search 1) 32; search 2) 57; search 3) 46; search 4) 88; search 5) 30; and search 6) 1. Initially, we identified 38 clinical trials in which one of the outcomes of interest was FES. However, 29 articles evaluated other modalities of prevention or treatment of FES, such as modified surgical techniques, and were excluded. Some of the studies employing corticosteroids in the prevention of FES were excluded for other reasons: two for using inclusion criteria that were too broad in scope[27,28]; and one for not specifically defining FES.[29] Table 1 describes the characteristics of the six studies included,[4,20-24] which involved a combined total population of 389 patients. For the meta-analysis, 368 patients were included.

The studies included were randomized, controlled clinical trials. Three studies used adequate allocation concealment[4,20,21] and, in one study, it was not possible to establish if there was allocation concealment.[23] Two studies used inadequate allocation concealment.[22,24] All studies used meth-

Table 1 - Characteristics of the studies.

Authorship Year of publication Country	Number and characteristics of the patients	Age (years)	Active treatment	Allocation concealment
Alho et al.[21] 1978 Finland	60 patients. At least two pelvic, femoral, or tibial fractures. Without severe lesions in other organs.	16-83	Methylprednisolone 10 mg/kg IV every 8 hours; total of 3 doses.	Adequate
Stoltenberg et al.[23] 1979 United States[a]	64 patients. Femoral or tibial fracture without lesions in other organs, without COPD or DM. Age below 65 years.	Mean, 29	Methylprednisolone 1 g every 8 hours; total of 3 doses.	Unclear
Schonfeld et al.[20] 1983 United States	62 patients. One or more diaphyseal fractures of a lower limb. Without accompanying lesions in other organs.	15-87	Methylprednisolone 7.5 mg/kg every 6 hours; total of 12 doses.	Adequate
Lindeque et al.[4] 1987 South Africa	55 patients. Femoral or tibial fracture with or without laceration of soft tissue. Without lesions in other organs or pre-existing pulmonary or cardiac diseases.	16-54	Methylprednisolone 30 mg/kg IV at admission and one dose repeated 4 hours later.	Adequate
Kallenbach et al.[22] 1987 South Africa	82 patients. One or more diaphyseal fractures of a lower limb. Without lesions in other organs or pre-existing pulmonary or cardiac diseases.	14-45	Methylprednisolone 1.5 mg/kg IV every 8 hours; total of 6 doses.	Inadequate
Babalis et al.[24] 2004 Greece	87 patients with isolated femoral or tibial fracture. Without lesions in other organs or pre-existing chronic diseases.	18-28	Methylprednisolone 1 mg/kg IV every 8 hours; total of 5 doses.	Inadequate

[a]The group receiving hypertonic glucose was excluded from the meta-analysis (n = 21); IV: intravenous; COPD: chronic obstructive pulmonary disease; and DM: diabetes mellitus.

ylprednisolone in the intervention group, and the treatment was initiated at hospital admission. The corticosteroid doses varied, and the last two studies used a much smaller dose.[22,24] The duration of treatment varied from 4 h to 3 days. Three studies used a placebo in the control group.[4,20,24] One study had three treatment arms: control group versus corticosteroid group versus hypertonic glucose group.[23] For meta-analysis, we excluded the hypertonic glucose group. In the other studies, the control group received standard care.[21,22] The follow-up period for the analysis of outcomes varied from 3 to 5 days. Although one patient was excluded from the corticosteroid group due to an incorrect dose, the corticosteroid and control groups were similar.[22]

The studies showed that the severity of the fractures was similar in the corticosteroid group and in the control group. Two studies quantified the severity of the fractures by using a scale.[20,23] In the study conducted by Schonfeld et al.,[20] femoral fracture was given a score of 4, whereas other types of fracture were given scores of 2 (for fractures of the femoral neck, pelvis, or tibia) or 1 (for fractures of the fibula). The mean score in the corticosteroid group was 4.19, compared with 4.49 in the placebo group.[20] In the study conducted by Stoltenberg et al.,[23] femoral fracture received a score of 2, tibial fracture received a score of 1, and other types of fractures received a score of 0.2. Patients in the corticosteroid group presented a mean score of 1.75, whereas those in the control group presented a mean score of 1.46. In that study, patients with femoral fracture were submitted to internal fixation 7 to 10 days after the fracture, when the criteria for the insertion of the intramedullary pin were met.[23]

In the study conducted by Babalis et al., in which 87 patients with closed or open grade I isolated fractures of the tibia or femur were analyzed, there were 19 closed femoral fractures, 41 closed tibial fractures, 10 open femoral fractures, and 17 open tibial fractures. All femoral fractures were treated with insertion of a intramedullary pin at 4 to 12 days after the trauma.[24] In the study conducted by Kallenbach et al., 82 patients suffered a total of 55 fractures of the femur, 33 fractures of the fibula/tibia, 7 fractures of the tibia, 1 fibular fracture, and 28 fractures in other parts; 72% of the patients were submitted to surgery within the first 5 days after the trauma.[22] The study conducted by Lindeque et al. analyzed patients with femoral or tibial fracture, with or without contusion and laceration of soft tissue, and the open and closed fractures were equally divided between the corticosteroid group and the control group.[4] In the study conducted by Alho et al., the mean frequency of diaphyseal fracture of the extremities/pelvic fracture was 2.5 per patient, and the majority of patients suffered femoral fracture.[21]

We performed a statistical analysis of two outcomes: FES and hypoxemia. However, we also reported the rates of complications and mortality in the studies. óThere was a variation in the definition of FES, although all of the studies considered one or more of the following clinical findings for the diagnosis: petechiae, respiratory failure/hypoxemia, and mental confusion. Lindeque et al.[4] proposed new diagnostic criteria based only on respiratory failure, but they also reported their results using a combination of the findings above. For the sake of uniformity, we used the results generated by a combination of the clinical findings described above. Hypoxemia was analyzed as a binary variable, and it was defined as what the authors of the clinical trials considered severe hypoxemia. Arterial oxygen tension < 60 mmHg was the criterion used in four studies.[4,20,21,24] Two other studies used different criteria and were therefore excluded from the hypoxemia analysis.[22,23]

In the isolated analysis of the relative risk of each study, they all showed a decrease in the risk of developing FES, but only two studies[21,22] reported a significant decrease (Figure 1 and Table 2).

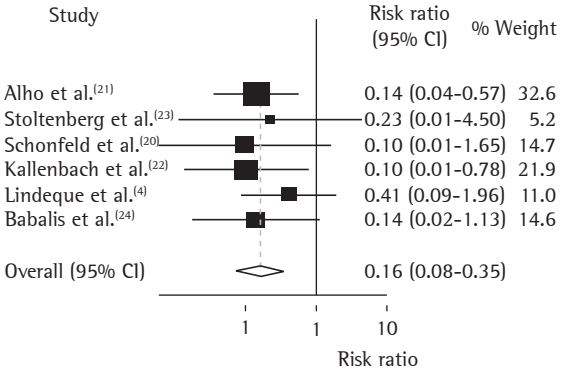

Figure 1 - Graphic representation (forest plot) of the meta-analysis of the effect of corticosteroids in preventing fat embolism syndrome. A relative risk < 1 favors corticosteroid; 95% CI: 95% confidence interval.

Table 2 - Relative risk of fat embolism syndrome, together with 95% confidence intervals, weight of each study, number of events/number of patients in each group.

Study	RR	95% CI	%Weight	Events/intervention	Events/control
Alho et al.[21]	0.14	0.04-0.57	32.6	2/29	15/31
Stoltenberg et al.[23]	0.23	0.01-4.49	5.2	0/20	2/23
Schonfeld et al.[20]	0.1	0.01-1.65	14.7	0/21	9/41
Kallenbach et al.[22]	0.11	0.01-0.78	21.9	1/40	10/42
Lindeque et al.[4]	0.41	0.09-1.96	11	2/27	5/28
Babalis et al.[24]	0.14	0.02-1.13	14.6	1/47	6/40
M-H pooled RR[a]	0.16	0.08-0.35			

[a]Pooled relative risk: $p < 0.001$; RR: relative risk; 95% CI: 95% confidence interval; and M-H: Mantel-Haenszel.

The pooled relative risk of developing FES was 0.16 (95% CI: 0.08-0.35) in the group receiving corticosteroids when compared with the control group ($p < 0.001$). The number of patients who needed to be treated with corticosteroids in order to prevent a case of FES was 5. There was no significant heterogeneity ($p = 0.87$). In the isolated analysis of the relative risk of each study, they all showed a decrease in the risk of developing hypoxemia, but only one study[4] reported a significant decrease (Figure 2 and Table 3). The pooled relative risk of developing hypoxemia was 0.34 (95% CI: 0.19-0.59) in the corticosteroid group when compared with the control group ($p < 0.001$). The number of patients who need to be treated with corticosteroids in order to prevent a case of hypoxemia was 5. There was no significant heterogeneity ($p = 0.75$).

The analysis of the four studies[4,20,21,23] that used higher doses of corticosteroids revealed a pooled relative risk of developing FES of 0.19 (95% CI: 0.07-0.47) in the corticosteroid group when compared with the control group ($p < 0.001$). The analysis of the two studies[22,24] that used lower doses of corticosteroids revealed a pooled relative risk of developing FES of 0.12 (95% CI: 0.03-0.51) in the corticosteroid group when compared with the control group ($p = 0.004$). In the two analyses, there was no significant heterogeneity.

We conducted an analysis from which we excluded the two studies[22,24] presenting inadequate allocation concealment. The analysis of four studies[4,20,21,23] revealed a pooled relative risk of developing FES of 0.19 (95% CI: 0.07-0.47) in the corticosteroid group when compared with the control group ($p < 0.001$). The analysis of three studies[4,20,21] revealed a pooled relative risk of developing hypoxemia of 0.38 (95% CI: 0.21-0.68) in the corticosteroid group when compared with the control group ($p = 0.001$). No significant heterogeneity was found in either of those two analyses.

Analysis using Begg's test[30] revealed that there was no significant publication bias ($p = 0.45$).

In the six studies, three deaths were reported. One diabetic patient in the corticosteroid group died after developing infection at the incision site. One patient in the control group died during the early intraoperative period and was excluded from the analysis.[22] One control group patient with chronic obstructive pulmonary disease died from respiratory failure.[20] Two corticosteroid group patients and four control group patients required mechanical ventilation.[21] Infection occurred in nine corticosteroid group patients and six control group patients.[20-22] There was one case of delayed fracture union in each group.[21]

Discussion

The analysis of evidence showed that corticosteroids decrease the risk of FES and hypoxemia after diaphyseal fracture. The analysis also showed that the decrease in the risk of FES was maintained with doses lower than those used in more recent studies.[22,24] These findings emphasize the importance of recognizing the patients at risk of developing FES. The typical patient is a young trauma victim aged 20-30 years who has suffered fracture of a lower limb. This is the age group traditionally more susceptible to greater trauma; however, there is no single and satisfactory explanation for the higher incidence in this age bracket.[31] Femoral fractures result in greater risk, and the incidence of FES increases with the number of fractures.[23] There are no biochemical markers of FES.

Table 3 - Relative risk of hypoxemia, together with 95% confidence intervals, weight of each study, number of events/number of patients in each group.

Study	RR	95% CI	%Weight	Events/intervention	Events/control
Alho et al.[21]	0.37	0.13-1.02	28.7	4/29	12/31
Schonfeld et al.[20]	0.39	0.09-1.62	17	2/21	10/41
Lindeque et al.[4]	0.39	0.18-0.86	39.5	6/27	16/28
Babalis et al.[24]	0.08	0.01-1.36	14.9	0/47[a]	5/40[a]
M-H pooled RR[b]	0.34	0.19-0.59			

[a]Data based on the third day after trauma; [b]pooled relative risk $p < 0.001$; RR: relative risk; and 95% CI: 95% confidence interval.

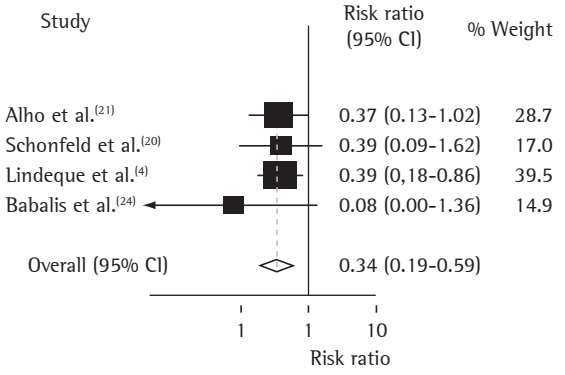

Figure 2 - Graphic representation (forest plot) of the meta-analysis of the effect of corticosteroids in preventing hypoxemia (arterial oxygen tension < 60 mmHg). A relative risk < 1 favors corticosteroid; 95% CI: 95% confidence interval.

Therefore, health professionals depend principally on the epidemiologic characteristics (age bracket) and clinical characteristics (area of fracture, type of trauma, and number of fractures) to evaluate the risk of developing FES.

The protective effect of corticosteroids against FES and hypoxemia suggests that the two are different stages of the same condition, hypoxemia being a subclinical form of FES.[4,22] The clinical manifestations of FES frequently appear 24-48 h after the trauma. However, in the studies evaluated, prophylaxis with corticosteroids was initiated at hospital admission.[4,20-24] There is no evidence that, after a diagnosis of FES has been established, specific therapy provides any benefit. Therefore, the treatment is based on clinical support.

The effect of corticosteroids might be better understood when the physiopathology of the disease is studied. Initially, the predominant theory was the mechanical one, i.e. FES would be the result of the mechanical obstruction of the pulmonary circulation by the fat globules. The most recent theory (the biochemical one) is based on the supposition that fatty acids or other mediators, free in the circulation or formed within the pulmonary circulation alone, might cause endothelial lesion and be directly toxic to the lung.[31,32] The effect of corticosteroids on FES might be related to the stabilization of the alveolar-capillary membrane/complement system, reduction of interstitial edema, and inhibition of the inflammatory response, as well as to delayed platelet aggregation.[33]

The reported number of patients who need to be treated in order to prevent a given event deserves careful interpretation. This number depends on the baseline risk of developing the disease.[34] Although the studies included in this meta-analysis have shown a mean baseline risk of developing FES after diaphyseal fracture of lower limb of 23%, the literature shows great variation, with numbers as low as 0.9%.[1]

The limitations of this study include those inherent to systematic reviews. For example, among clinical trials, only half of those presented as abstracts at conferences are later published. This publication bias tends to affect principally the studies with negative results.[35] In addition, there is evidence that smaller clinical trials are more susceptible to publication bias.[36] However, we carried out an analysis of publication bias and there was no statistical significance. Although there were two studies in which the allocation concealment was considered inadequate,[22,24] the effect of the corticosteroids was maintained in a subanalysis that excluded those two studies. The studies varied as to the duration of corticosteroid administration, which makes it impossible to determine the exact duration of treatment required in order to obtain a preventive effect. In addition, there was pronounced variation

in the corticosteroid dose. However, a subanalysis of the two recent studies[22,24] in which a lower dose was used revealed that the effect of reducing the risk of FES was maintained.

The available evidence is insufficient to determine whether the use of corticosteroids decreases (or increases) the risk of more relevant clinical outcomes such as mechanical ventilation requirement or even death. We suggest opting for lower doses as in the study conducted by Babalis et al. (Table 1).[24] The use of corticosteroids in diabetic patients and individuals with immunosuppressant diseases should be avoided. It is also important to emphasize that the effect demonstrated does not apply to polytraumatized patients, since these were excluded from the clinical trials.

We conclude that the data currently available demonstrate that the use of corticosteroids reduces the incidence of FES and hypoxemia in adult patients who have suffered isolated diaphyseal fracture of a lower limb.

References

1. Bulger EM, Smith DG, Maier RV, Jurkovich GJ. Fat embolism syndrome. A 10-year review. Arch Surg. 1997;132(4):435-9.
2. Hofmann S, Huemer G, Salzer M. Pathophysiology and management of the fat embolism syndrome. Anaesthesia. 199853(Suppl 2):35-7.
3. Ganong RB. Fat emboli syndrome in isolated fractures of the tibia and femur. Clin Orthop Relat Res. 1993;(291):208-14.
4. Lindeque BG, Schoeman HS, Dommisse GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. J Bone Joint Surg Br. 1987;69(1):128-31.
5. Scroggins C, Barson PK. Fat embolism syndrome in a case of abdominal lipectomy with liposuction. Md Med J. 1999;48(3):116-8.
6. Apostolou CD, Skourtas CE, Tsifetakis SD, Papagelopoulos PJ. Fat embolism after uncemented total hip arthroplasty. Clin Orthop Relat Res. 2002;(398):153-6.
7. Schulz F, Trübner K, Hildebrand E. Fatal fat embolism in acute hepatic necrosis with associated fatty liver. Am J Forensic Med Pathol. 1996;17(3):264-8.
8. Horowitz I, Klingenstein RJ, Levy R, Zimmerman MJ. Fat embolism syndrome in delirium tremens. Am J Gastroenterol. 1977;68(5):476-80.
9. Eckardt P, Raez LE, Restrepo A, Temple JD. Pulmonary bone marrow embolism in sickle cell disease. South Med J. 1999;92(2):245-7.
10. McDermott ID, Culpan P, Clancy M, Dooley JF. The role of rehydration in the prevention of fat embolism syndrome. Injury. 2002;33(9):757-9.
11. Pinney SJ, Keating JF, Meek RN. Fat embolism syndrome in isolated femoral fractures: does timing of nailing influence incidence? Injury. 1998;29(2):131-3.
12. Riska EB, von Bonsdorff H, Hakkinen S, Jaroma H, Kiviluoto O, Paavilainen T. Prevention of fat embolism by early internal fixation of fractures in patients with multiple injuries. Injury. 1976;8(2):110-6.
13. Svenningsen S, Nesse O, Finsen V, Hole A, Benum P. Prevention of fat embolism syndrome in patients with femoral fractures--immediate or delayed operative fixation? Ann Chir Gynaecol. 1987;76(3):163-6.
14. Kim YH, Oh SW, Kim JS. Prevalence of fat embolism following bilateral simultaneous and unilateral total hip arthroplasty performed with or without cement: a prospective, randomized clinical study. J Bone Joint Surg Am. 2002;84-A(8):1372-9.
15. Pitto RP, Hamer H, Fabiani R, Radespiel-Troeger M, Koessler M. Prophylaxis against fat and bone-marrow embolism during total hip arthroplasty reduces the incidence of postoperative deep-vein thrombosis: a controlled, randomized clinical trial. J Bone Joint Surg Am. 2002;84-A(1):39-48.
16. Pitto RP, Blunk J, Kössler M. Transesophageal echocardiography and clinical features of fat embolism during cemented total hip arthroplasty. A randomized study in patients with a femoral neck fracture. Arch Orthop Trauma Surg. 2000;120(1-2):53-8.
17. Pitto RP, Schramm M, Hohmann D, Kössler M. Relevance of the drainage along the linea aspera for the reduction of fat embolism during cemented total hip arthroplasty. A prospective, randomized clinical trial. Arch Orthop Trauma Surg. 1999;119(3-4):146-50.
18. Pitto RP, Koessler M, Kuehle JW. Comparison of fixation of the femoral component without cement and fixation with use of a bone-vacuum cementing technique for the prevention of fat embolism during total hip arthroplasty. A prospective, randomized clinical trial. J Bone Joint Surg Am. 1999;81(6):831-43.
19. Kröpfl A, Berger U, Neureiter H, Hertz H, Schlag G. Intramedullary pressure and bone marrow fat intravasation in unreamed femoral nailing. J Trauma. 1997;42(5):946-54.
20. Schonfeld SA, Ploysongsang Y, DiLisio R, Crissman JD, Miller E, Hammerschmidt DE, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. Ann Intern Med. 1983;99(4):438-43.
21. Alho A, Saikku K, Eerola P, Koskinen M, Hämäläinen M. Corticosteroids in patients with a high risk of fat embolism syndrome. Surg Gynecol Obstet. 1978;147(3):358-62.
22. Kallenbach J, Lewis M, Zaltzman M, Feldman C, Orford A, Zwi S. 'Low-dose' corticosteroid prophylaxis against fat embolism. J Trauma. 1987;27(10):1173-6.
23. Stoltenberg JJ, Gustilo RB. The use of methylprednisolone and hypertonic glucose in the prophylaxis of fat embolism syndrome. Clin Orthop Relat Res. 1979;(143):211-21.
24. Babalis GA, Yiannakopoulos CK, Karliaftis K, Antonogiannakis E. Prevention of posttraumatic hypoxaemia in isolated lower limb long bone fractures with a minimal prophylactic dose of corticosteroids. Injury. 2004;35(3):309-17.
25. The Cochrane Collaboration [homepage on Internet].Oxford: Cochrane Handbook for Systematic Reviews of Interventions [updated 30 January 2007; cited 31 January 2007]. Available from: http://www.cochrane.org/resources/handbook
26. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22(4):719-48.
27. Lepistö P, Avikainen V, Alho A, Jäättelä A, Karaharju E, Kataja J, et al. Fat embolism in severely injured patients. Ann Chir Gynaecol Fenn. 1975;64(4):198-202.

28. Rokkanen P, Alho A, Avikainen V, Karaharju E, Kataja J, Lahdensuu M, et al. The efficacy of corticosteroids in severe trauma. Surg Gynecol Obstet. 1974;138(1):69-73.
29. Shier MR, Wilson RF, James RE, Riddle J, Mammen EF, Pedersen HE. Fat embolism prophylaxis: a study of four treatment modalities. J Trauma. 1977;17(8):621-9.
30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101.
31. ten Duis HJ. The fat embolism syndrome. Injury. 1997;28(2):77-85.
32. Mudd KL, Hunt A, Matherly RC, Goldsmith LJ, Campbell FR, Nichols GR 2nd, et al. Analysis of pulmonary fat embolism in blunt force fatalities. J Trauma. 2000;48(4):711-5.
33. Mellor A, Soni N. Fat embolism. Anaesthesia. 2001;56(2):145-54.
34. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med. 1997;126(9):712-20.
35. Verstraete M. Value and limitation of meta-analysis. Pathophysiol Haemost Thromb. 2002;32(5-6):278-81. Erratum in: Pathophysiol Haemost Thromb. 2003;33(3):172.
36. Pogue J, Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. Lancet. 1998;351(9095):47-52.