

Future Perspectives: The Need for Large Clinical Trials

Clary J. Foote, MD,* Sheila Sprague, MSc,*‡ Emil H. Schemitsch, MD, FRCSC,†
and Mohit Bhandari, MD, PhD, FRCSC*‡

Summary: Fragility fractures represent a growing problem with large economic and patient burdens that are likely to increase as the population ages. The elderly patient with osteopenic bone presents a unique surgical challenge with appreciable risks associated with each surgical treatment option. As demonstrated in this supplement, the current evidence suggests that the best surgical treatment options for patients with fragility fractures remains largely unknown. Additional evidence, from large clinical trials, is required before definitive treatment recommendations can be made in many cases. In this article, we review the example of the femoral neck fracture to illustrate this point.

Key Words: osteoporosis, fragility fractures, femoral neck fractures, future directions

(*J Orthop Trauma* 2011;25:S95–S98)

INTRODUCTION

Despite years of investigation into the prevention and treatment of fragility fractures, controversy regarding the optimal medical and surgical treatments persists. As discussed in multiple articles within this supplement, large gaps in evidence exist in the diagnosis and treatment of fragility fractures. Although the questions that remain unanswered may vary across fracture types, we have used the femoral neck fracture in the current article as an example to demonstrate the current gap in definitive evidence. Recommended treatment options for femoral neck fractures have been based on fracture pattern, activity level, and chronologic age with less emphasis on bone quality and a lack of standardized patient subgroups in the randomized trials conducted to date.^{1–4} Commonly used treatment options include multiple methods of internal fixation, total joint replacement, and partial joint replacement.

Accepted for publication March 21, 2011.

From the *Division of Orthopaedics, Department of Surgery, McMaster University, Hamilton, Ontario, Canada; †Division of Orthopaedic Surgery, Department of Surgery, University of Toronto, Toronto, Ontario, Canada; and ‡Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

No funds were received in support of this work.

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

Reprints: Mohit Bhandari, MD, PhD, FRCSC, Chair, Division of Orthopaedic Surgery, Department of Surgery, McMaster University, 293 Wellington Street North, Suite 110, Hamilton, Ontario L8L 8E7, Canada (e-mail: bhandam@mcmaster.ca).

Copyright © 2011 by Lippincott Williams & Wilkins

Although multiple research initiatives have been successfully completed, they have produced conflicting results, and the definitive answer to the optimal treatment of femoral neck fractures remains elusive.

Does the Choice of Implant Impact Outcome of Internal Fixation?

Despite intensive investigation comparing internal fixation with arthroplasty, optimal approaches for internal fixation have largely been ignored.⁵ Most of the trials comparing different internal fixation implants are derived from indirect comparisons of trials of arthroplasty versus internal fixation. Bhandari et al recently conducted a meta-analysis¹ that found a trend toward fewer fracture healing complications with sliding hip screws (SHS) when compared with three cancellous screws (odds ratio, 0.76; 95% confidence interval, 0.47–1.25). On the contrary, a prior meta-analysis by Parker et al, which included a review of 25 randomized controlled trials, found no significant difference in healing or complication rates among internal fixation techniques. A subsequent Cochrane Review⁶ found increased operative time and blood loss with SHS but no significant differences in complications and healing. Several trials that have directly compared outcomes between SHS versus cancellous screws/pins in nondisplaced^{7,8} and displaced fractures^{9–11} have demonstrated trends toward reduced revision rates with SHS. As a result of contradictory findings and methodological limitations, it can be argued that a definitive answer to the question of whether the choice of implant impacts the outcome of internal fixation remains unanswered. To address this important question, a large international randomized controlled trial called the Fixation using Alternative Implants for the Treatment of Hip Fractures (FAITH) has been initiated to assess key outcomes after standardized internal fixation techniques with either a SHS or cancellous screws.¹²

Is Arthroplasty More Efficacious Than Internal Fixation of Displaced Femoral Neck Fractures?

Internal fixation of displaced (Garden III and IV) femoral neck fractures has been associated with high rates of osteonecrosis and reoperation.¹ Several meta-analyses,^{1,13,14} randomized controlled trials,^{15–17} and prospective studies¹⁸ comparing internal fixation with arthroplasty have been conducted. Bhandari et al¹ performed a meta-analysis of 14 randomized controlled trials assessing outcomes of surgery for displaced femoral neck fractures. This meta-analysis found that revision rates were significantly reduced with arthroplasty when compared with internal fixation (relative risk, 0.23; 95% confidence interval, 0.13–0.42), but there were trends toward

increased mortality (relative risk, 1.27; 95% confidence interval, 0.84–1.92) and significant increases in blood loss and infection after arthroplasty. Dai et al also recently conducted a meta-analysis that compared internal fixation with arthroplasty in cognitively intact, mobile, elderly patients.¹⁴ This meta-analysis found lower reoperation and complication rates after arthroplasty compared with internal fixation but also found a trend toward greater mortality at 1 year. Another meta-analysis by Rogmark et al¹³ reported similar results as Dai et al with a trend toward greater mortality at 30 days but not at 1 year postsurgery. Discrepancies between these meta-analyses indicate that it is not known whether the optimal treatment is arthroplasty or internal fixation.

Additional large multicenter trials are necessary before a definitive treatment recommendation can be made.

Does Arthroplasty Type Impact Outcome?

Total hip arthroplasty (THA)¹⁹ and hemiarthroplasty (HA)²⁰ have both been shown to be viable options in the treatment of displaced femoral neck fractures. Initial studies raised concerns over high rates of dislocation,²¹ loosening,²² and medical complications^{23,24} in THA and acetabular wear²⁵ after HA in high-demand patients. These studies shaped surgeons' initial reluctance toward concurrent acetabular replacement.²⁶ However, advancements in THA, particularly larger femoral head size and uncemented femoral components,

TABLE 1. Current Clinical Trials Investigating Efficacy of Surgical Treatment of Fragility Femoral Neck Fractures

Trial	Status	Description
Using Alternative Implants for the Surgical Treatment of Hip Fractures (the FAITH Study)	Recruiting	Prospective multicenter randomized control trial assessing revision rates, functional outcomes, and complications of sliding hip screw versus cannulated screw fixation in ambulatory patients over 50 years with low-energy displaced or undisplaced femoral neck fractures
Hemiarthroplasty or Internal Fixation for Displaced Femoral Neck Fractures—5 Years Follow Up	Active 2-year follow-up of patients has been completed	A multicenter randomized control trial assessing functional outcomes, quality of life, and reoperation rates of bipolar hemiarthroplasty versus two cannulated screw fixation for displaced femoral neck fractures in patients older than 60 years previously ambulatory
Dynamic Internal Fixation of Femoral Neck Fractures (DIFINE)	Recruiting	Prospective cohort study evaluating complication rates and functional outcomes of dynamic hip screw fixation with side plate versus Targon FN (up to six screw fixation and side plate) in patients older than 55 years previously ambulatory for fractures that require operative management
Functional Status, Morbidity and Mortality in Cemented Versus Press-Fit Hemiarthroplasty	Completed	A randomized control trial comparing press-fit to cemented arthroplasty for displaced subcapital hip fractures with outcomes including 1-year mortality, event rates of myocardial infarction or unstable angina in the immediate postoperative period (1 week), and ability to do activities of daily living; patients were older than 55 years and had a pre-morbid walking distance of over 10 feet
Feasibility and Safety Study of rhBMP-2/CPM for Hip Fractures	Completed	Prospective randomized control trial comparing internal fixation alone (cannulated screws, sliding hip screw, or cephalomedullary nail) versus internal fixation and rhBMP-2/CPM for displaced femoral neck or intertrochanteric hip fractures; inclusion was patients older than 55 years and anatomic reductions only; main outcome was secondary fracture displacement
Warwick Hip Trauma Study: A Randomised Clinical Trial Comparing Interventions to Improve Outcomes in Internally Fixed Intracapsular Fractures of the Proximal Femur	Recruiting	Prospective single-center randomized control trial comparing standard internal fixation alone (three cannulated screws) versus standard internal fixation and platelet-rich plasma (PRP) versus internal fixation with Targon FN (side plate and up to six head screws); inclusion was "all patients," including those with cognitive impairment, admitted with an intracapsular (displaced or undisplaced) fracture; outcomes included reoperation and radiographic union at 12 months
Comparing THA and HA on Revision Surgery and Quality of Life in Adults With Displaced Hip Fractures (the HEALTH Study)	Recruiting	Prospective multicenter randomized control trial assessing revision surgery, functional, and quality-of-life outcomes of THA versus HA (unipolar or bipolar) in low-energy displaced femoral neck fractures in mobile patients older than 50 years; the study used an expert-based design

THA, total hip arthroplasty; HA, hemiarthroplasty.

show promise to reduce complications after THA in active elderly patients. Blomfeldt et al²⁷ randomized 120 lucid, active elderly patients to either HA or THA and reported significantly better Harris hip scores at 1 year with no difference in complications, dislocations, or mortality. Another randomized controlled trial by Keating et al² again showed better functional outcomes in THA with no difference in mortality at 24 months. Recently, Hopley et al²⁸ performed a meta-analysis comparing THA with HA (unipolar and bipolar), which included seven randomized controlled trials, three quasirandomized trials, and eight retrospective cohort studies. This study reported reduced reoperation rates and better functional improvements after THA than HA. Notably, their pooled analyses of four recent randomized controlled trials^{2,26,27,29} with the highest methodological quality suggested no significant impact of type of arthroplasty on reoperation rates and showed trends favoring HA for dislocations, deep infections, and general complications. Among two of the studies that reported functional outcomes,^{26,27,29} functional gains with THA were superior. Unfortunately, this analysis encountered methodological issues such as lack of concealment, heterogeneity of study inclusion criteria, and type of HA. The difficulties incurred by pooling available evidence support the need for large, valid trials of high methodological quality. Currently, the HEALTH trial (Hip Fracture Evaluation with Alternatives of THA versus HA), an international multicenter randomized controlled trial comparing THA and HA in elderly patients with displaced femoral neck fractures, is underway to provide meaningful data on the optimal treatment for patients with displaced femoral neck fractures.¹²

What Is the Role of Osteobiologics in the Treatment of Femoral Neck Fractures?

Osteobiologics are materials or agents that may promote fracture healing and enhance fracture stability. Given the challenges presented by femoral neck fragility fractures, osteobiologics may provide some benefit. Unfortunately, there has been limited clinical research conducted to date of the efficacy of osteobiologics and the treatment of femoral neck fractures.³⁰ Different osteobiologics have been developed and investigated, including allograft bone, calcium phosphate cement, osteoinductive growth factors (bone morphogenetic proteins and platelet derived growth factors) and systemic agents such as parathyroid hormone. Basic science research on osteobiologics has shown promising results; however, few clinical trials have been conducted and the results of the trials conducted to date have been contradictory and inconclusive.³⁰ Additional clinical trials are required before clinical recommendations can be made on the efficacy of osteobiologics in patients with femoral neck fractures.

CONCLUSIONS

Despite being among the most common and debilitating orthopaedic injuries, optimal treatment for fragility femoral neck fractures remains elusive. As described, many patient-important questions remain unanswered in the treatment of femoral neck fractures. Fortunately, multiple high-quality research initiatives on the treatment of femoral neck fractures

are ongoing (Table 1). International multicenter trials will play a primary role in resolving current controversy and enabling evidence-based tailoring of surgical care for patients with fragility femoral neck fractures.

The questions and concerns raised in this article can easily be translated to other types of fragility fractures. The current evidence is inconclusive regarding the optimal treatment methods for fragility fractures in general. Similar methodological limitations also exist in the research conducted to date in this area as evident by the articles in this supplement. Multiple diagnostic, prognostic, and treatment questions remain unanswered. Additional high-quality clinical trials are necessary before definitive recommendations can be made and patient care improved. We are hopeful with additional large, international initiatives that many of the unanswered questions will become known in the years to come.

REFERENCES

- Bhandari M, Devereaux PJ, Swiontkowski MF, et al. Internal fixation compared with arthroplasty for displaced fractures of the femoral neck. A meta-analysis. *J Bone Joint Surg Am.* 2003;85:1673–1681.
- Keating JF, Grant A, Masson M, et al. Randomized comparison of reduction and fixation, bipolar hemiarthroplasty, and total hip arthroplasty. Treatment of displaced intracapsular hip fractures in healthy older patients. *J Bone Joint Surg Am.* 2006;88:249–260.
- Heetveld MJ, Rogmark C, Frihagen F, et al. Internal fixation versus arthroplasty for displaced femoral neck fractures: what is the evidence? *J Orthop Trauma.* 2009;23:395–402.
- Heetveld MJ, Raaymakers EL, van Eck-Smit BL, et al. Internal fixation for displaced fractures of the femoral neck. Does bone density affect clinical outcome? *J Bone Joint Surg Br.* 2005;87:367–373.
- Bhandari M, Tornetta P 3rd, Hanson B, et al. Optimal internal fixation for femoral neck fractures: multiple screws or sliding hip screws? *J Orthop Trauma.* 2009;23:403–407.
- Parker MJ, Stockton G. Internal fixation implants for intracapsular proximal femoral fractures in adults. *Cochrane Database Syst Rev.* 2001; 4:CD001467.
- Kuokkanen H, Korkala O, Antti-Poika I, et al. Three cancellous bone screws versus a screw-angle plate in the treatment of Garden I and II fractures of the femoral neck. *Acta Orthop Belg.* 1991;57:53–57.
- Wu CC, Chen WJ. Minimally displaced intra-capsular femoral neck fractures in the elderly—comparison of multiple threaded pins and sliding compression screws surgical techniques. *J Orthop Surg (Hong Kong).* 2003;11:129–136.
- Madsen F, Linde F, Andersen E, et al. Fixation of displaced femoral neck fractures. A comparison between sliding screw plate and four cancellous bone screws. *Acta Orthop Scand.* 1987;58:212–216.
- Paus A, Gjengedal E, Hareide A, et al. Dislocated fractures of the femoral neck treated with von Bahr screws or hip compression screw. Results of a prospective, randomized study. *J Oslo City Hosp.* 1986;36:55–61.
- Parmar V, Kumar S, Aster A, et al. Review of methods to quantify lag screw placement in hip fracture fixation. *Acta Orthop Belg.* 2005;71:260–263.
- Bhandari M, Sprague S, Schemitsch E. Resolving controversies in hip fracture care: the need for large collaborative trials in hip fractures. *J Orthop Trauma.* 2009;23:479–484.
- Rogmark C, Johnell O. Primary arthroplasty is better than internal fixation of displaced femoral neck fractures: a meta-analysis of 14 randomized studies with 2,289 patients. *Acta Orthop.* 2006;77:359–367.
- Dai Z, Li Y, Jiang D. Meta-analysis comparing arthroplasty with internal fixation for displaced femoral neck fracture in the elderly. *J Surg Res.* 2011;165:68–74.
- Blomfeldt R, Tornkvist H, Ponzer S, et al. Internal fixation versus hemiarthroplasty for displaced fractures of the femoral neck in elderly patients with severe cognitive impairment. *J Bone Joint Surg Br.* 2005;87:523–529.
- Rogmark C, Carlsson A, Johnell O, et al. A prospective randomised trial of internal fixation versus arthroplasty for displaced fractures of the neck of the femur. Functional outcome for 450 patients at two years. *J Bone Joint Surg Br.* 2002;84:183–188.

17. Leonardsson O, Sernbo I, Carlsson A, et al. Long-term follow-up of replacement compared with internal fixation for displaced femoral neck fractures: results at ten years in a randomised study of 450 patients. *J Bone Joint Surg Br.* 2010;92:406–412.
18. Bjorgul K, Reikeras O. Hemiarthroplasty in worst cases is better than internal fixation in best cases of displaced femoral neck fractures: a prospective study of 683 patients treated with hemiarthroplasty or internal fixation. *Acta Orthop.* 2006;77:368–374.
19. Ravikumar KJ, Marsh G. Internal fixation versus hemiarthroplasty versus total hip arthroplasty for displaced subcapital fractures of femur—13 year results of a prospective randomised study. *Injury.* 2000;31:793–797.
20. Haidukewych GJ, Israel TA, Berry DJ. Long-term survivorship of cemented bipolar hemiarthroplasty for fracture of the femoral neck. *Clin Orthop Relat Res.* 2002;403:118–126.
21. Dorr LD, Glousman R, Hoy AL, et al. Treatment of femoral neck fractures with total hip replacement versus cemented and noncemented hemiarthroplasty. *J Arthroplasty.* 1986;1:21–28.
22. Greenough CG, Jones JR. Primary total hip replacement for displaced subcapital fracture of the femur. *J Bone Joint Surg Br.* 1988;70:639–643.
23. Parvizi J, Ereth MH, Lewallen DG. Thirty-day mortality following hip arthroplasty for acute fracture. *J Bone Joint Surg Am.* 2004;86:1983–1988.
24. Sim FH, Stauffer RN. Management of hip fractures by total hip arthroplasty. *Clin Orthop Relat Res.* 1980;152:191–197.
25. van Vugt AB, Oosterwijk WM, Goris RJ. Osteosynthesis versus endoprosthesis in the treatment of unstable intracapsular hip fractures in the elderly. A randomised clinical trial. *Arch Orthop Trauma Surg.* 1993;113:39–45.
26. Bhandari M, Devereaux PJ, Tornetta P 3rd, et al. Operative management of displaced femoral neck fractures in elderly patients. An international survey. *J Bone Joint Surg Am.* 2005;87:2122–2130.
27. Blomfeldt R, Tornkvist H, Eriksson K, et al. A randomised controlled trial comparing bipolar hemiarthroplasty with total hip replacement for displaced intracapsular fractures of the femoral neck in elderly patients. *J Bone Joint Surg Br.* 2007;89:160–165.
28. Hopley C, Stengel D, Ekkernkamp A, et al. Primary total hip arthroplasty versus hemiarthroplasty for displaced intracapsular hip fractures in older patients: systematic review. *BMJ.* 2010;340:c2332.
29. Baker RP, Squires B, Gargan MF, et al. Total hip arthroplasty and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck. A randomized, controlled trial. *J Bone Joint Surg Am.* 2006;88:2583–2589.
30. Nauth A, Miclau T, Bhandari M, et al. The use of osteobiologics in the treatment of fragility fractures. *J Orthop Trauma.* In press.