M. H. A. Malik · J. Gray · P. R. Kay

Early aseptic loosening of cemented total hip arthroplasty: the influence of non-steroidal anti-inflammatory drugs and smoking

Accepted: 3 March 2004 / Published online: 27 March 2004
© Springer-Verlag 2004

Abstract The purpose of this study was to investigate whether the clinical variables of non-steroidal anti-inflammatory drugs (NSAID) usage and cigarette smoking are possibly linked to aseptic loosening around total hip arthroplasty (THA). We performed a retrospective review of the records and radiographs of 224 patients attending for follow-up at Wrightington Hospital between August 2002 and 2003 who had undergone THA. The following information was recorded: age, gender, primary and revision surgery details, radiographic parameters, smoking history and NSAID usage history. Logistic regression analysis was used to determine if there is any statistically significant association between NSAID usage or smoking habit and aseptic loosening. No such association was found.

Résumé Le but de cette étude était de chercher si les variables cliniques que sont l'usage d'anti-inflammatoires non stéroïdiens (AINS) et la consommation de cigarettes pouvaient être liées au descellement aseptique d'une arthroplastie de la hanche. Nous avons fait une étude rétrospective des registres et des radiographies de 224 malades revus dans l'Institution entre août 2002 et 2003 et qui avait subi une arthroplastie totale de la hanche. Les informations suivantes ont été enregistrées: âge, genre, détails de la chirurgie primaire et de la chirurgie de révision, paramètres radiographiques, histoire de la consommation tabagique et de l'usage d'AINS. L'analyse

régressive a été utilisée pour déterminer s'il y avait une association statistiquement notable entre l'usage d'AINS ou l'habitude de fumer et le descellement aseptique. Aucune association n'a été trouvée.

Introduction

The principle cause of failure of total hip arthroplasty (THA) is periprosthetic osteolysis [10]. This is believed to be a biological response to sub-micrometre-sized particulate debris, the bulk of which is polyethylene particles generated by wear at the articulating surfaces [14]. It is believed that phagocytosis of these wear particles leads to cytokine production resulting in increased proliferation and differentiation of osteoclast precursors into mature osteoclasts [23]. Most of the cytokines involved in bone resorption around THAs are pro-inflammatory: TNF- α , IL-1 α , IL-1 β , IL-6 and PGE₂ [3].

One area of intense research into the basic science of aseptic loosening is that of the regulation of cyclooxygenase, a prostanoid-converting enzyme, by cytokines, which may be the mechanism of production of the inflammatory component of aseptic loosening in cemented THA [2, 22]. This may be of great clinical relevance, as non-steroidal anti-inflammatory drugs (NSAIDs) are inhibitors of cyclooxygenase activity and are therefore potential therapeutic agents in the prevention of aseptic loosening. Indeed, cell culture studies have demonstrated the effectiveness of such drugs in reducing prostanoid production and bone resorption [7].

Acute periprosthetic bone loss occurs after THA [19], there commonly being a loss of 10–45% of the periprosthetic bone mass during the first few years [5, 18]. The relationship between adaptive bone loss and aseptic loosening of THA remains unclear, but preliminary data has demonstrated enhanced bone loss in the latter as compared to the former [15]. Environmental factors exert a significant influence on bone loss with increasing age in men and women. Numerous studies have demonstrated that cigarette smoking is such a risk factor for decreased bone

M. H. A. Malik · J. Gray · P. R. Kay
Centre for Hip Surgery,
Wrightington Hospital,
Hall Lane, Appley Bridge, Wigan, WN6 9EP, UK

M. H. A. Malik
Centre for Integrated Genomic Research, Stopford Building,
The University of Manchester,
Oxford Road, Manchester, M13 9TP, UK

M. H. A. Malik (✉)
14 The Boulevard, Didsbury Point, Manchester, M20 2EU, UK
e-mail: hammymalik@hotmail.com
Tel.: +44-161-2320487

density of the proximal femur [17, 24]. The purpose of this study was to investigate whether the clinical variables of NSAID usage and cigarette smoking are possibly linked to aseptic loosening around THAs.

Patients and methods

We performed a retrospective review of the records and radiographs of all patients attending for follow-up at Wrightington Hospital between August 2002 and 2003 who had undergone THA. This was as part of another prospective study investigating patient-related factors and aseptic loosening. Strict inclusion and exclusion criteria were set for the study group (aseptically loosened THA) and the control group (well-fixed implants) to make them directly comparable. Only Caucasian patients of either gender with a primary diagnosis of osteoarthritis were included. All had a cemented Charnley monoblock femoral stem and a cemented polyethylene acetabular cup. Radio-opaque cement was used in all cases.

Early aseptic loosening for both components was defined as that occurring within 6 years of implantation in line with the yearly incidence of loosening in relation to the evolution of the Charnley low-friction arthroplasty [20]. Acetabular cup loosening was defined either by findings at revision surgery or by type 3 (complete demarcation in all DeLee and Charnley zones [4]) or type 4 (socket migration) radiographic demarcation using the criteria of Hodgkinson et al. [12]. Femoral-stem aseptic loosening was defined either by findings at revision surgery, the definite radiographic loosening criteria of Harris [11] or progressive endosteal cavitation across zones as described by Gruen [9]. Well-fixed control THAs were defined as those that had remained clinically asymptomatic for over 10 years and demonstrated none of the described radiographic features of aseptic loosening or 'at risk' signs as described by Wroblewski et al. [20].

All patients were interviewed in the clinic. The following information was recorded: age, gender, primary and revision surgery details, radiographic parameters as detailed above, smoking history and NSAID usage history. Statistical analysis was performed using SPSS software with the level of significance set at 0.05. The confidence interval (CI) and odds ratios were determined with the CI set at 95%. Associations were investigated with contingency tables using Fisher's exact and chi-squared tests. A logistic regression model was then used to analyse data.

Results

Of 274 notes found to be suitable for inclusion, 224 patients were recruited to the study for whom complete data sets were available. One hundred and forty-three were recruited to the control group with a mean time of THR survival of 14.6 years, and 81 were recruited to the aseptic

Table 1 Smoking habit of patients in both groups

Group	Non-smoker	Smoker	Ex-Smoker
Aseptic	49	10	32
Control	79	15	40

Table 2 Non-steroidal anti-inflammatory drug (NSAID) usage of patients in both groups

Group	No pre-op NSAID	Pre-op NSAID	No post-op NSAID	Post-op NSAID
Aseptic	47	34	51	30
Control	96	47	101	42

Table 3 Risk factor associations. NSAID non-steroidal anti-inflammatory drug

Predictor	P value
Smoking	0.201
Ex-smoker	0.075
Pre-op NSAID	0.066
Post-op NSAID	0.075

group with a mean time to THR failure of 5.1 years. The mean age of all patients was 69.2 years (70.9 in the control group and 66.2 in the aseptic group). There were 129 women and 94 men. The differences in age and gender between groups was not statistically significant. One hundred and thirty patients had never smoked, 69 were ex-smokers and 25 were smokers (average of 15.5 cigarettes/day). The effect of smoking on the incidence of aseptic loosening is shown in Table 1. Percentage of smokers was 13.6% in the study group and 10.5% in the control group. The use of NSAIDs is shown in Table 2. Diclofenac and ibuprofen accounted for 80.7% of all NSAID use. The average duration of NSAID usage pre-operatively was 3.4 years and post-operatively 4.4 years. Predictors of primary interest derived from the statistical model are summarised in Table 3. Using the logistic regression model, number of cigarettes smoked, years as a non-smoker and length of usage of NSAID were not found to be associated with aseptic loosening.

Discussion

NSAIDs are the most commonly prescribed drug class in the world [1]. They have been found to adversely affect prostaglandin-mediated bone remodelling in vitro and in animals in a dose-dependent fashion [8]. However, they may also inhibit the production of cytokines that mediate osteolysis. Both present and past smoking habits have been found to be risk factors for proximal femoral osteoporosis [21, 25], and it is known that active bone remodelling and localised osteoporosis occur after prosthetic implantation in this region [15].

In this study, we looked to see if there is a relationship between these proposed factors and the development of aseptic loosening in THA. We found no such statistically significant relationship with regards to smoking habit as a risk factor or NSAID usage as either a protective or risk factor. This is the first study we are aware of that has looked at the possible effects of NSAID usage in this context. It would appear that no change in prescribing practice of NSAIDs can be recommended on the basis of the results from this study. Two previous studies have produced conflicting evidence as to the significance

of smoking habit [6, 13], but smoking should still be strongly discouraged due to its health risks and effect of increased resource consumption and poorer short-term outcome following joint replacement[16].

This study is limited by its being retrospective and its moderate sample size, but the method of logistic regression analysis is a widely accepted statistical method of looking for associations. The two groups studied were quite distinct in terms of outcome but were otherwise comparable in terms of implant, surgical technique, age, gender and demographics. It may be that effects from NSAID usage and smoking habit are not seen with early aseptic loosening but can contribute to later loosening, and this possibility should be investigated.

Acknowledgements MHAM is the recipient of a Wellcome Trust Entry Level Clinical Training Fellowship and The Royal College of Surgeons of England Laming Evans Research bursary.

References

- Baum C, Kennedy DL, Forbes MB (1985) Utilization of non-steroidal anti-inflammatory drugs. *Arthritis Rheum* 28:686–692
- Buttery LDK, Hukkanen MVJ, O'Donnell A, et al (1995) Nitric oxide dependent and independent induction of prostaglandin synthesis in osteoblasts. *Bone* 17:560–566
- Chiba J, Rubash HE, Kim KJ, Iwaki Y (1994) The characterisation of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. *Clin Orthop* 300:304–312
- DeLee JG, Charnley J (1976) Radiographic demarcation of cemented sockets in total hip replacement. *Clin Orthop* 121:20–26
- Engh CA, McGovern TF, Bobyn JD, Harris WH (1992) A quantitative evaluation of periprosthetic bone-remodeling after cementless total hip arthroplasty. *J Bone Joint Surg [Am]* 72:109–120
- Espehaug B, Havelin LI, Engesaeter LB, Langeland N, Vollset SE (1997) Patient-related risk factors for early revision of total hip replacements. A population register-based case-control study of 674 revised hips. *Acta Orthop Scand* 68:207–215
- Glant TT, Jacobs JJ, Mikecz K, et al (1996) Particulate-induced prostaglandin- and cytokine-mediated bone resorption in an experimental system and in failed joint replacements. *Am J Ther* 3:27–41
- Glassman SD, Rose SM, Dimar JR, et al (1998) The effect of postoperative nonsteroidal anti-inflammatory drug administration on spinal fusion. *Spine* 23:834–838
- Gruen TA, McNeice GM, Amstutz HC (1979) "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop* 141:17–27
- Harris WH (1995) The problem is osteolysis. *Clin Orthop* 311:46–53
- Harris WH, McCarthy JC, O'Neill DA (1982) Femoral component loosening using contemporary techniques of femoral cement fixation. *J Bone Joint Surg [Am]* 64:1063–1067
- Hodgkinson JP, Shelley P, Wroblewski BM (1988) The correlation between the roentgenographic appearance and operative findings at the bone-cement junction of the socket in Charnley low friction arthroplasties. *Clin Orthop* 228:105–109
- Inoue K, Ushiyama T, Tani Y, Hukuda S (1999) Sociodemographic factors and failure of hip arthroplasty. *Int Orthop* 23:330–333
- Jacobs JJ, Roebuck KA, Archibeck M, et al (2001) Osteolysis: basic science. *Clin Orthop* 393:71–77
- Krogger H, Venesmaa P, Jurvelin J, Miettinen H, Suomalainen O, Alhava E (1998) Bone density at the proximal femur. *Clin Orthop* 352:66–74
- Lavernia CJ, Sierra RJ, Gomez-Marin O (1999) Smoking and joint replacement: resource consumption and short-term outcome. *Clin Orthop* 367:172–180
- Nguyen TV, Kelly PJ, Sambrook PN, et al (1994) Lifestyle factors and bone density in the elderly: Implications for osteoporosis prevention. *J Bone Miner Res* 9:1339–1346
- Ninimäki J, Jalovaara P (1995) Bone loss from the proximal femur after arthroplasty with an isoelastic femoral stem. BMD measurements in 25 patients after 9 years. *Acta Orthop Scand* 66:347–351
- Okano T, Hagino H, Otsuka T, et al (2002) Measurement of periprosthetic bone mineral density by dual-energy X-ray absorptiometry is useful for estimating fixation between the bone and the prosthesis in an early stage. *J Arthroplasty* 17:49–55
- Pacheco V, Shelley P, Wroblewski BM (1988) Mechanical loosening of the stem in Charnley arthroplasties. *J Bone Joint Surg [Br]* 70:596–599
- Rapuri PB, Gallagher JC, Balhorn KE, Ryschon KL (2000) Smoking and bone metabolism in elderly women. *Bone* 27:429–436
- Salvemini D, Misko TP, Masferrer JL, et al (1993) Nitric oxide activates cyclooxygenase enzymes. *Proc Natl Acad Sci USA* 90:7240–7244
- Silva MJ, Sandell LJ (2002) What's new in orthopaedic research. *J Bone Joint Surg [Am]* 84:1490–1496
- Slemenda CW, Christian JC, Reed T, et al (1992) Long-term bone loss in men: Effects of genetic and environmental factors. *Ann Intern Med* 117:286–291
- Tanaka T, Latorre MRDO, Jaime PC, Florindo AA, Pippa MGB, Zerbin CAF (2001) Risk factors for proximal femur osteoporosis in men aged 50 years or older. *Osteoporosis Int* 12:942–949