International Orthopaedics (SICOT) (2004) 28:142–145
DOI 10.1007/s00264-004-0539-0

ORIGINAL PAPER

Levente Gáspár · Balázs Dezső · Zoltán Csernátony · Lilla Gáspár · János Szabó · Zoltán Szekanecz · Kálmán Szepesi · Klára Matesz

Capsular neuronal elements and their relation to pain reduction and functional improvement following total hip replacement

Accepted: 14 January 2004 / Published online: 5 February 2004

Abstract We studied changes of pain intensity and functional impairment in 22 patients with osteoarthrosis undergoing total hip replacement. Using a visual analogue scale, the mean scores for pain and disability before surgery were 71.7 and 70.9 respectively. Both scores showed gradual improvement during a 1-year follow-up period, with more than 90% of the total improvement occurring within the first 3 months. After 1 year, the scores for pain and disability were 11.9 and 4.1 respectively. The hip joint capsule was studied using immunohistochemistry to detect neurofilaments. Neurofilament immunoreactivity was observed in 16/22 cases and was correlated with pain and disability scores. However, there were no correlations between pre- and postoperative pain scores, the score changes, and the quantity of capsular neurofilaments. Thus, other factors than capsular neurofilaments influence the scores of pain and disability in osteoarthritis.

Résumé Nous avons étudié les changements d'intensité de la douleur et les modifications fonctionnelles chez 22 malades ayant subit une prothèse totale de la hanche pour arthrose. Avec une échelle analogue visuelle, les scores moyens pour la douleur et l'invalidité avant la chirurgie étaient de 71.7 et 70.9 respectivement. Les deux scores ont montré l'amélioration graduelle pendant une année après l'opération, avec plus de 90% de l'amélioration totale dans les trois premiers mois. Après une année les scores pour douleur et invalidité étaient de 11.9 et 4.1 respectivement. La capsule articulaire a été étudiée par immunohistochimie pour détecter les neurofilaments. L'immunoréactivité des neurofilaments a été observé dans 16/22 cas et était corrèlée avec la douleur et le score de l'invalidité. Cependant, il n'y avait pas de corrélations entre les scores de la douleur pré- et postopératoire, la modification du score fonctionnel et la quantité de neurofilaments capsulaires. Il y a donc d'autres facteurs que les neurofilaments capsulaires qui influencent la douleur et l'invalidité dans l'arthrose.

L. Gáspár (✉) · Z. Csernátony · J. Szabó · K. Szepesi
Department of Orthopaedic Surgery,
Medical Health and Science Center,
University of Debrecen,
Nagyerdei krt 98, 4012 Debrecen, Hungary
e-mail: lgaspar@jaguar.dote.hu
Tel.: +36-52-415494
Fax: +36-52-415494

B. Dezső
Department of Pathology, MHSC,
University of Debrecen,
Debrecen, Hungary

L. Gáspár · Z. Szekanecz
3rd Department of Medicine, Rheumatology Division-MHSC,
University of Debrecen,
Debrecen, Hungary

K. Matesz
Department of Anatomy, MHSC,
University of Debrecen,
Debrecen, Hungary

Introduction

Pain is an essential symptom of osteoarthritis (OA). Chronic pain in OA often leads to disability. Both pain and disability may be indications for total hip replacement (THR) and may influence the final outcome of the operation [8]. Therefore, one of the most important aims is to relieve pain. Non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used, cause only temporarily relief and can cause severe complications [5, 9]. In patients with severe, destructive OA, only THR can diminish pain and improve physical function and quality of life. In addition, the intensity of pain may predict the final outcome of the THR: the more the pain, the poorer the outcome [12].

Irrespective of the underlying mechanisms, joint pain is usually associated with the activation of nociceptors, or free nerve endings, of the neighbouring tissues [13]. Thus, apart from other biochemical mechanisms, the presence and quantity of neuronal elements in the joint capsule

may also be involved in the pathogenesis of pre- or post-operative pain.

In this study, we evaluated changes in pain intensity and functional impairment in patients with OA undergoing THR. These two indicators were correlated with each other, as well as with the quantity of neuronal elements, such as neurofilaments (NF), in the capsule of the affected joint. In addition, the possible involvement of mast cells, key players in inflammation and pain, was investigated.

Materials and methods

Patients and tissue samples

Twenty-two patients undergoing THR due to severe OA were arbitrarily selected for this study. In every patient, the joint capsule with the synovial membrane was subtotally removed during surgery and fixed in 4% phosphate-buffered paraformaldehyde solution (pH 7.4) overnight. Small pieces of tissue were then washed in 0.1 M phosphate buffer and then in 10 and 20% sucrose dissolved in the same buffer solution. Sixty-micrometre frozen sections were cut in a cryostat and processed for immunohistochemistry.

Immunohistochemistry

Sections were incubated with monoclonal antibody anti-NF 200 (Sigma) for 2 days at 4°C and then transferred into a solution of mouse avidin-biotinylated peroxidase complex for 4 h at room temperature. Immunoreactivity was developed using nickel-enhanced diaminobenzidine (DAB) chromogen reaction. In cases of positive immunoreactivity for NF, further immunohistochemical analysis was carried out using antibodies detecting substance P (SP; INSTAR), calcitonin-gene-related peptide (CGRP; Peninsula Labs), and neurokinin 1 (NK1; Sigma). Immunoreactions using non-specific IgG were used as negative controls.

Samples showing no immunoreactivity with NF were assigned a score of 0. Those showing positive reaction were scored using a 1–5 semiquantitative scale according to the density of nerve fibres per microscopic field. In all specimens, dimethyl-methylene blue (DMMB; PolyScience) staining was performed at 1.5 pH to detect mast cells.

Evaluation of pain and disability

A visual analogue scale (VAS) of 100 mm was used to assess the intensity of pain and the functional impairment of the patients. All patients were assessed at five time points: before surgery, 2 weeks and 3, 6 and 12 months after surgery. We correlated pain and disability scores with each other, as well as with the score of NF in the joint capsule.

Statistical analysis

Paired *t*-test, Pearson correlation and independent samples tests were used to detect significant differences and correlations. *P* values <0.05 were considered as statistically significant.

Results

Before surgery, most patients suffered from severe pain. The mean pre-operative pain score was 71.7 mm. The decrease in pain intensity was significant at every time point after the THR. VAS score was 27.9 mm, 17.4 mm, 15.8 mm and 11.9 mm at 2 weeks, 3, 6 and 12 months, respectively. This reflects a 61%, 75%, 78% and 83% pain reduction at various time points, respectively ($P<0.05$) (Fig. 1). During the follow-up period, pain scores showed gradual improvement, but the scale of improvement was not even. The major pain decrease occurred within the first 3 months (Table 1, Fig. 1).

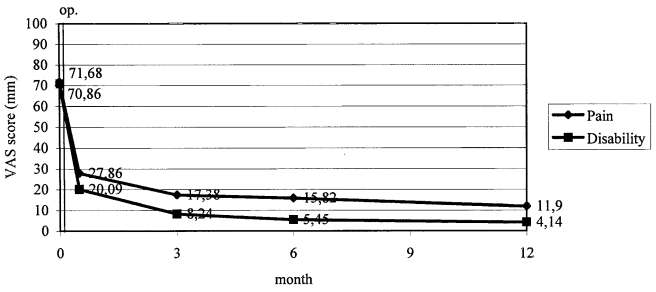

Fig. 1 Changes of the pain and disability mean visual analogue scale (VAS) scores

OA also caused severe functional impairment in these patients: the mean pre-operative VAS disability score was 70.9 mm. Improvement after the operation was significant at every time point: the VAS disability score was 20.1 mm, 8.2 mm, 5.5 mm and 4.1 mm at 0.5, 3, 6 and 12 months, respectively. These scores reflect 71.7%, 88.4%, 92.2% and 94.2% reductions in disability at the above-mentioned time points, respectively ($P<0.05$) (Fig. 1). The decrease in the mean disability score was more pronounced than in the case of the pain score. Again, functional status improved mostly in the first 3 post-operative months.

Parallel comparison of pain and disability VAS scores was carried out during the four follow-up periods. Pearson's correlation test showed strong correlation during the first and second follow-up periods (R: 0.786 and 0.684), while some correlation was found during the third (R: 0.476) and none during the final (R: −0.281) follow-up interval.

Positive NF immunoreactivity was observed in 16/22 cases indicating the presence of nerve fibres in the capsule tissue. Smaller and larger bundles of nerve fibres of different diameters were detected both in the dense connective tissue of joint capsule and in the synovial membrane (Fig. 2). In many cases, some of the small calibre fibres left the bundles and formed a delicate network or plexus in the loose connective tissue. These fibres may represent the free nerve endings, located quite frequently in close vicinity to the blood vessels. The density of the nerve fibres varied in the specimens. More than half of the NF-positive specimens had scores between 3 and 5. Positive immunoreactivity with CGRP, SP and NK1 was detected in most of the NF-positive tissues. In these cases, immunoreactivity was detected in the small calibre fibres, the majority of which were located around the blood vessels.

Table 1 Quantity of nerve fibres, pain and disability expressed in scores

Patient	Nerve fibres	Pain score					Disability score				
		Pre-op.	Post-op.				Pre-op.	Post-op.			
			2 weeks	3 months	6 months	12 months		2 weeks	3 months	6 months	12 months
1	0	62	35	26	18	15	41	12	15	6	10
2	0	51	21	9	0	3	82	27	2	0	0
3	1	30	20	25	22	18	11	8	7	10	2
4	0	81	21	19	0	0	96	0	11	0	0
5	1	89	77	34	52	73	82	76	13	55	30
6	1	98	40	20	12	3	80	20	13	10	9
7	0	94	20	0	0	0	85	13	0	0	0
8	2	78	45	9	0	0	63	34	0	0	0
9	1	78	47	0	0	0	87	45	0	0	0
10	1	89	17	15	0	0	90	13	9	0	0
11	0	80	23	24	65	48	100	40	20	20	24
12	4	45	15	18	10	6	35	3	5	0	0
13	3	71	26	0	0	0	65	18	0	0	0
14	5	52	18	11	15	0	48	15	0	0	0
15	5	85	52	35	21	17	73	25	9	0	10
16	4	75	43	40	21	18	60	0	0	0	0
17	5	75	25	19	10	13	61	40	30	4	2
18	5	76	4	15	20	0	95	2	0	0	0
19	0	69	19	15	10	2	68	21	20	5	0
20	2	86	0	0	0	0	99	10	0	0	0
21	1	45	27	40	37	31	60	0	0	0	0
22	5	68	18	31	35	3	78	20	19	10	0

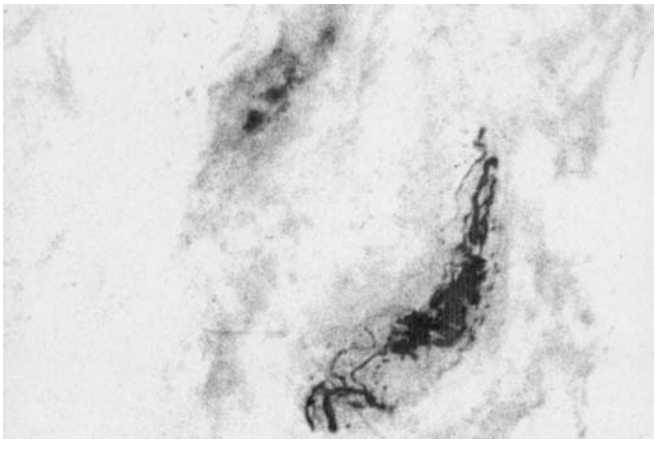

Fig. 2 Neurofilament-positive fibres in the joint capsule. ×20

DMMB staining showed violet-purple granules in the cytoplasm of some round-shaped cells. The metachromatic staining is characteristic for mast cells. Mast cells were located predominantly in the loose connective tissue, in many cases next to the small blood vessels. Mast cells were present in all tissues studied, but their number was higher in NF-positive specimens. In many cases, scattered metachromatic granules were present in the extra-cellular part of the tissue indicating degranulation of mast cells.

However, the number of capsular NF (semiquantitative NF score) did not show any significant correlation with scores of pre- and post-operative pain or disability or with changes in scores.

Discussion

OA is accompanied by pain and functional impairment. In several cases, there is great discrepancy between the pre-operative hyperalgesia, functional impairment of the patient and the structural damage [4]. The pre-operative radiographic stage of OA is of no predictive value for the post-operative outcome of THR [11]. One possible source of pain may be the mechanical and chemical irritation caused by derangement of articular cartilage, the high tension of the articular capsule produced by an increased amount of synovial fluid [6], and the increased intra-osseous pressure [1, 10].

Joint inflammation accompanying OA causes peripheral and central sensitisation. Peripheral sensitisation is produced by the action of inflammatory mediators such as prostaglandins, neuropeptides, bradykinin and cytokines, which activate the nociceptors [17]. Some cytokines increase the production of NGF in various connective tissue cells including the mast cells [16]. NGF exerts a modulatory role on sensory nociceptive neurons and seems to be correlated with the hyperalgesia occurring in tissue inflammation [16, 19]. Our present results suggest that the large number of mast cells in the NF-positive specimens may be associated with this process. In the NF-positive specimens, the small calibre showed a positive immunoreaction for SP, CGRP and NK1. These fibres may represent A delta and C fibres associated with the pain sensation. In chronic neuropathic pain, one of the receptors of the SP, the NK1, is upregulated [7, 20]. The complex neuronal activation involves not only local sensitisation of joint nociceptors but also modifications in central pain pathways [13, 17]. Muscle hyperalgesia and

extended pain areas might be due to central sensitisation caused by painful OA [2].

THR implantation decreases the pain and improves the quality of life [3]. In our study, significant improvement of pain and disability was observed in all patients. However, no correlation was found between the intensity of pre-operative pain, functional impairment and quantity of NF in the capsule of the operated hip. These findings seem to be different from those published by Rabinowicz et al. This group found correlation between the nerve lesions of the synovial membrane and the capsule and the existence or absence of hip pain [14]. In their opinion, the nerves are preserved for a long time despite progressive surrounding lesions, and this fact may explain the persistence of pain [15].

According to our present findings, pain accompanying OA cannot be explained by the presence or absence and quantity of NF in the joint capsule. This fact is supported by the results after minimal invasive hip replacement [18]. Pain decrease is significant even after minimally invasive procedures although the joint capsule is not removed.

Acknowledgements This study was supported by a grant from the Hungarian Medical Research Council (60/2000). We express special thanks to Katalin Hodosi, Béláné Szanitter Magdolna Hajdú and László Kiss for their kind assistance.

References

1. Arnoldi CC, Djurhuus JC, Heerfordt J, Karle A (1980) Intraosseous phlebography, intraosseous pressure measurements and 99mTC-polyphosphate scintigraphy in patients with various painful conditions in the hip and knee. Acta Orthop Scand. 51:19–28
2. Bajaj P, Bajaj P, Graven-Nielsen T, Arendt-Nielsen L (2001) Osteoarthritis and its association with muscle hyperalgesia: an experimental controlled study. Pain. 93:107–114
3. Berend ME, Thong AE, Faris GW, Newbern G, Pierson JL, Ritter MA (2003) Total joint arthroplasty in the extremely elderly: hip and knee arthroplasty after entering the 89th year of life. J Arthroplasty 18:817–821
4. Birrell F, Croft P, Cooper C, Hosie G, Macfarlane G, Silman A (2000) Health impact of pain in the hip region with and without radiographic evidence of osteoarthritis: a study of new attenders to primary care. The PCR Hip Study Group. Ann Rheum Dis. 59:857–863
5. Denk H (2002) Drug-induced liver injury. Verh Dtsch Ges Pathol 86:120–125
6. Goddard NJ, Gosling PT (1988) Intra-articular fluid pressure and pain in osteoarthritis of the hip. J Bone Joint Surg Br. 70:52–55
7. Hernanz A, De Miguel E, Romera N, Perez-Ayala C, Gijon J, Arnalich F (1993) Calcitonin gene-related peptide II, substance P and vasoactive intestinal peptide in plasma and synovial fluid from patients with inflammatory joint disease. Br J Rheumatol. 32:31–35
8. Knutsson S, Engberg IB (1999) An evaluation of patients' quality of life before, 6 weeks and 6 months after total hip replacement surgery. J Adv Nurs. 30:1349–1359
9. Laine L (2003) Gastrointestinal effects of NSAIDs and coxibs. J Pain Symptom Manage. 25(Suppl 2):32–40
10. Mao BY (1993) The change of intraosseous pressure in the femur and tibia near knee and knee pain. Zhonghua Wai Ke Za Zhi 31:593–595
11. Nilsdotter AK, Aurell Y, Siosteen AK, Lohmander LS, Roos HP (2001) Radiographic stage of osteoarthritis or sex of the patient does not predict one year outcome after total hip arthroplasty. Ann Rheum Dis. 60:228–232
12. Nilsdotter AK, Petersson IF, Roos EM, Lohmander LS (2003) Predictors of patient relevant outcome after total hip replacement for osteoarthritis: a prospective study. Ann Rheum Dis. 62:923–930
13. Perrot S, Guilbaud G (1996) Pathophysiology of joint pain. Rev Rhum Engl Ed. 63:485–492
14. Rabinowicz T, Jacqueline F (1980) Lesions of the nerves of the hip involving chronic rheumatic infections (ankylosing spondylitis, rheumatoid arthritis, arthrosis). Anatomopathologic study. Rev Rhum Mal Osteoartic. 47:37–44
15. Rabinowicz T, Jacqueline F (1990) Pathology of the capsular and synovial hip nerves in chronic hip diseases. Pathol Res Pract. 186:283–292
16. Safieh-Garabedian B, Poole S, Allchorne A, Winter J, Woolf CJ (1995) Contribution of interleukin-1 beta to the inflammation-induced increase in nerve growth factor levels and inflammatory hyperalgesia. Br J Pharmacol 115:1265–1275
17. Schaible HG, Ebersberger A, Von Banchet GS (2002) Mechanisms of pain in arthritis. Ann N Y Acad Sci. 966:343–354
18. Sherry E, Egan M, Warnke PH, Henderson A, Eslick GD (2003) Minimal invasive surgery for hip replacement: a new technique using the NILNAV hip system. ANZ J Surg. 73:157–161
19. Skaper SD (2001) Nerve growth factor: a neurokine orchestrating neuroimmune-endocrine functions. Mol Neurobiol. 24:183–199
20. Sluka KA, Milton MA, Willis WD, Westlund KN (1997) Differential roles of neurokinin 1 and neurokinin 2 receptors in the development and maintenance of heat hyperalgesia induced by acute inflammation. Br J Pharmacol. 120:1263–1267