VASCULAR PROLIFERATION AND NSAIDS IN THE TORN ROTATOR CUFF

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Introduction

The rotator cuff is subject to constant pressure from the head of the humerus. This tends to ‘wring out’ the blood supply resulting in a functionally avascular critical zone, although microvessels can be identified. This zone is the site of degeneration and tears. Attempts at repair under these circumstances could be compromised by inadequate local function of the vascular system particularly sprouting of the capillaries to support the repair process.

In previous work we have identified differences in microvessel distribution according to tissue location, being absent from areas with clear signs of advanced matrix degeneration and increased, relative to the resected edge, in some areas with indications of repair attempts, e.g. fibroblast hypercellularity and random collagen deposition. Widespread vascular endothelial growth factor (VEGF) positivity was observed in fibroblast and endothelial cell populations and diffusely within the matrix. Strong positivity of the cell cycle inhibitor p27 (cyclin-dependent kinase inhibitor p27) was observed in many endothelial cells. Thus the endothelial cells appeared to be simultaneously under both a mitogenic, a VEGF drive, and subject to an inhibition of proliferation i.e. p27 positivity (Rawal et al. 2002).

Non-steroidal anti-inflammatory drug (NSAID) administration is very common in patients with rotator cuff tears. NSAIDs block prostaglandin synthesis and impair healing of gastrointestinal ulcers and growth of colonic tumours, in part by inhibiting angiogenesis particularly that induced by hypoxia (Jones et al. 1999, & 2002). Their mechanism of action involves inhibition of the enzyme cyclo-oxygenase (COX) resulting in inhibition of prostaglandin biosynthesis. However, they have also been shown to up-regulate p27 in vascular smooth muscle cells and in endothelial cells.

Objective

Does NSAID administration influence ongoing endothelial cell proliferation in torn rotator cuff?

Methods

Fifty three patients undergoing surgical repair for rotator cuff tears were included in this study. Rotator cuff tissue obtained at debridement was formalin fixed and paraffin embedded. The resected edge was identified by a paint mark. Pathological assessment was performed on H & E stained sections. The sections were studied for areas of increased vascularity as compared with the resected edge. This ongoing vascular proliferation was differentiated from a pre-existing increase in vascular density by identification of plump endothelial cells and budding of vessels.

Patient data, tear size and duration of symptoms, was extracted from case records. Drug prescription data was obtained from the patient’s notes as well as by telephone conversation with general practitioners regarding the repeat prescription of analgesic drugs prior to the surgery. The drugs used by the patient were grouped as follows 1) Total analgesia = NSAIDs & COX 2 inhibitors & Opiates, 2) Total NSAIDs = NSAIDs + COX-2 Inhibitors, 3) NSAIDs excluding only COX-2 Inhibitor administration, 4) Opiates (Codeine). NSAIDs included Aspirin, Ibuprofen and Diclofenac. Of these 53 patients 35 were taking repeat prescription analgesics for pain relief. 18 patients were not taking prescription analgesics, however, data on self medication was not sought. 25 patients were taking NSAIDs of which 18 patients were also taking codeine. 23 patients were taking codeine, of which 6 were not taking NSAIDs. Six patients were taking COX-2 inhibitors.

The data obtained were analysed using SPSS for drug administration according to patient details, tear details and finally for a correlation between the vascularity of the rotator cuff and the use of NSAIDs. The statistical tests used were Mann-Whitney U, Chi-square and Pearson correlation coefficient as appropriate.

Results

Patients’ age ranged from 41 to 87 years, mean of 63.6 years, 30 female and 23 male. The duration of symptoms ranged from 3 months to 18 years and the size of the rotator cuff tear ranged from 1-5 cm. There was no significant difference between the size of the tear, age of patient or duration of symptoms between those patients taking analgesia and those not, nor between the type of analgesia used. Histopathological examination revealed no ongoing inflammation in the debrided tissues, as indicated by the absence of lymphocytes and macrophages. There was no significant correlation between the duration of symptoms, age of patients and the size of the rotator cuff tear on the vascularity and ongoing vascular proliferation in the debrided tissue.

Thirty three patients showed evidence of preexisting increased vascular density. In 22 patients frequent plump endothelial cells indicative of ongoing vascular proliferation were identified and in 16 a pre-existing increase in vascular density. Nine patients demonstrated both no pre-existing or ongoing increase in vascular density.

Of the 35 patients taking analgesics, vascular proliferation was absent or reduced in 22 (63%). 20 of these patients were taking non-steroidal anti-inflammatory drugs. Four patients were taking only COX-2 inhibitor drugs, all these patients had increased vascularity with evidence of ongoing vascular proliferation in the debrided tissue. Of twenty three patients taking NSAIDs excluding COX-2 inhibitors 19 demonstrated no ongoing vascular proliferation (p=0.000). Of seven patients taking only NSAIDs excluding COX-2 inhibitors none demonstrated ongoing vascular proliferation. Twenty three patients were taking codeine based analogies. Of ten patients using codeine without NSAIDs 8 demonstrated active ongoing vascular proliferation (p=0.027). Of 18 patients using NSAIDs and codeine 13 demonstrated on ongoing vascular proliferation (p=0.023).

Discussion

In this group of patients with full thickness rotator cuff tears, for whom surgery was considered suitable, there is clear evidence that administration of NSAIDS interferes with endothelial cell proliferation. Following our previous study, these data expands the understanding of endothelial cell proliferation in the torn rotator cuff. The mechanisms of action are unclear, and indeed in 20% of patients taking NSAIDS ongoing vascular proliferation was observed. If, however, endothelial cell proliferation is a significant component of repair both in the early and possibly post-operative stages of a rotator cuff problems, more work should be done to clarify this matter.

Summary

A significant correlation was found between the use of non-steroidal anti inflammatory drugs excluding COX-2 inhibitors and reduced vascular proliferation. Patients taking NSAIDs showed a significant reduction in ongoing vascular proliferation, including when taken in combination with opiate analogics.

References

• Rawal A, Roebuck M.M., Rossi M.L., Helliwell T.R, Frostick S.P. Vascularity in torn rotator cuff. JBJS (Br) 2002 In press