Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Research Article

ROLE OF CELECOXIB IN BENIGN BREAST DISEASE: RANDOMISED CONTROL TRIAL

Soumen Das[1], Retina Paul[2]
[1]Assistant Professor, Department of Surgery, IPGMER & SSKM Hospital, Kolkata, India
[2]Post Graduate Trainee, Department of Microbiology, Dr. D.Y.Patil Medical College, Pune, India
*Dr. Soumen Das, MBBS, MS, FUICC, Assistant Professor, Department of Surgery, IPGMER & SSKM Hospital, Kolkata, India, Email: drsoumen_das@yahoo.co.in

Received on:25/03/12 Revised on: 28/04/12 Accepted on: 22/06/12

ABSTRACT:
Benign Breast Disease (BBD), commonest cause of morbidity in females due to breast diseases, still offers therapeutic challenge. Several drug therapies (with Evening Primrose Oil, Danazol etc) have been tried, but none made gold standard. Reports on effect of Cox-2 inhibitors are scarce. This randomized control trial aims at determination of effect of Cox- inhibitors (Celecoxib) in BBD in comparison to Evening Primrose Oil (EPO). Celecoxib showed better reduction in lump size (in 80%) than EPO group (in 50%). Pain reduction was excellent in COX -2 groups as compared to EPO group. Recurrence rate was also lower in Celecoxib group at 10 weeks. Side effects were almost nil in both the groups. Celecoxib is better than EPO in the management of BBD. Short course therapy with COX-2 inhibitors gives good pain relief, greater reduction in lump size, low recurrence with minimum side effects.
Keyword: Benign breast disorders, Celecoxib

INTRODUCTION:

BBD frequently encountered by women especially of premenopausal age group. Aberration of Normal Development and Involution (ANDI) classification system is being popularly used to classify BBD since most benign disorders are related to normal process of reproductive life. Management of most BBD is primarily nonsurgical. Varieties of drugs are in use like Evening Primrose Oil (EPO), Bromocriptine, Danazol, Tamoxifen etc. However, no aforementioned medications have achieved such efficacy to be labeled as the gold standard. Data on role of COX-2 inhibitors in BBD are scarce. Few studies demonstrate expression of COX-2 enzymes in breast cancer and other benign breast neoplasm[1, 3]. Over expression of COX-2 is associated with reduced apoptosis[2], increased Vascular Endothelial Growth Factor (VEGF) production and angiogenesis[5]. All of these mechanisms help in breast tissue proliferation. Therefore, our hypothesis was- COX-2 inhibitors will act on BBD.

MATERIALS AND METHODS:

A total of 4036 patients with BBD were randomly divided into two groups. Study was carried out as per the ethical guidelines (Institutional Ethical Committee proposal clearance- 1712009). Patients with clinical, radiological, histological evidence of BBD above 16 years but premenopausal were included in this study. Patient with known cardiac (viz- hypertension), renal impairment, history of peptic ulcer disease, benign lesions that are high risk for breast cancer excluded from this study. One group (n=2018) received conventional EPO (1 g twice daily for 6 weeks) other group received COX -2 inhibitors (Celecoxib 200 mg twice daily for 6 weeks). Effect was monitored by reduction in breast lump size and breast pain (Cardiff Breast Score) [14] at 6weeks, 8 weeks and 10 weeks. Cardiff breast score (CBS) is a popular method to assess the response to therapy in a patient with mastalgia. CBS I indicates an excellent response, CBS II and III indicate substantial and poor response respectively, whereas CBS IV indicates no response. A total of 200 patients were lost in follow- up. Statistical analyses were made with Epi-info.

RESULTS:

Demographic data shows patients of both groups were between 16-40 years and the age distribution of both the groups is depicted in Figure 1. Lump size reduction was better in COX-2 group (Table 1). Pain reduction (measured by Cardiff Breast Pain Score) was better in COX-2 group (Table 2). In both the groups, there were no drug related side effects. Only one patient in COX-2 group developed epigastric pain that subsided after medication with proton pump inhibitor. Recurrence was measured by either increase in lump size or increase in pain. This was 60% in EPO group and 20% in COX-2 group.

DISCUSSION:

Benign disorders of breast are common. Its spectrum extends from ANDI to breast cysts. Various medical treatments are in practice. EPO, Bromocriptine, Danazol, Tamoxifen are used commonly and quite effectively but none achieved the gold standard. COX enzyme has 2 isoforms COX-1 and COX-2 [8]. COX-1 is constitutively expressed in most tissues[6], and is responsible for physiological housekeeping functions such as platelet aggregation and gastric cytoprotection[2]. Over-expression of COX-2 has been detected in over 70% of *in situ* and invasive breast tumours in addition to a wide variety of solid epithelial tumours including the colon, lung, prostate, skin, esophagus, pancreas and bladder[7]. Over-expression of COX-2 has been shown to promote angiogenesis[2] and cell proliferation[7, 10] and inhibit apoptosis[5]. In invasive breast cancer, high levels of COX-2 expression are associated with a significantly poorer disease free survival compared with patients whose tumours express low or no COX-2 [9,10], and high levels of COX-2 correlate with an increased risk of recurrence in the pre-invasive breast cancer ductal carcinoma *in situ* (DCIS). This data substantiates the effect of COX-2 in cell proliferation and tumourogenesis. Inhibition of COX-2 leads to reduced proliferation *in vivo*. Celecoxib is a potent anti-angiogenic agent. Over-expression of COX-2 leads to increased vascular endothelial growth factor receptor (VEGF) production[11, 12] and COX-2 inhibition leads to a reduction in VEGF[13]. All these mechanisms help COX-2 inhibitors to act against BBD. In comparison to EPO, it has shown better

lump reduction, better pain reduction, and lower recurrence with negligible side effects.

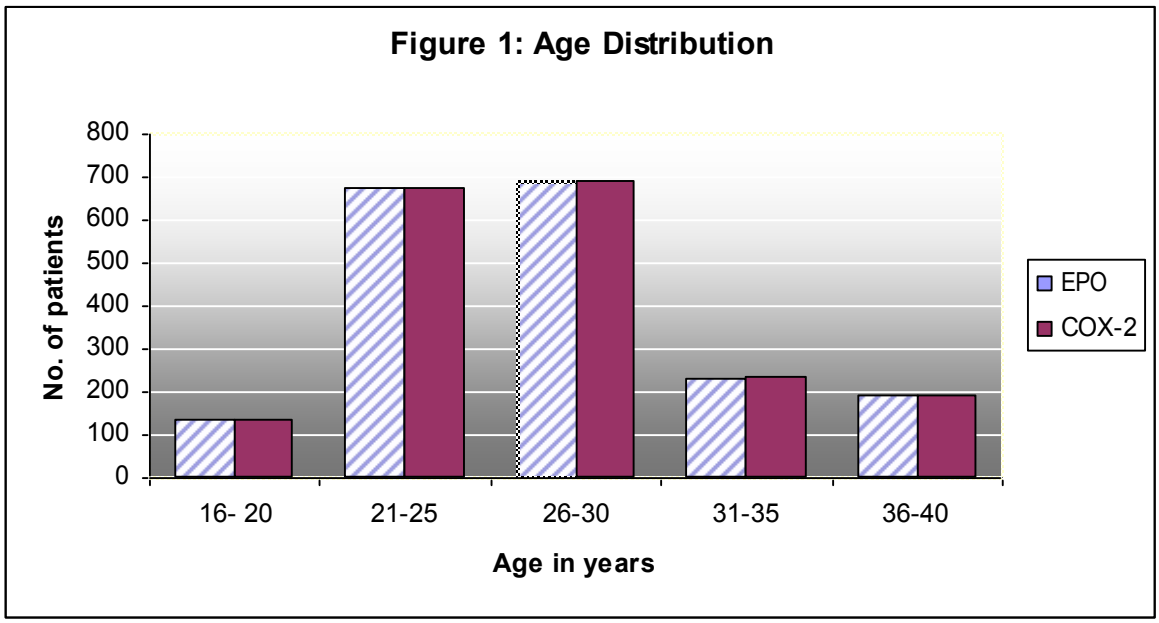
CONCLUSION:

COX-2 inhibitors are better than EPO in the management of BBD. Short-course therapy with COX-2 inhibitors gives good pain relief, greater reduction in lump size, low recurrence with negligible side effects. This study recommends the use of COX-2 inhibitors (Celecoxib) in BBD as a primary therapy, non-responders to EPO. Whether co-administration of COX-2 inhibitors with EPO is associated with synergistic effect or not, further randomized trials are essential to find the answer.

Conflict of interest: None

REFERENCES:

1. Hla T, Bishop-Bailey D, Liu CH, *et al*. Cyclooxygenase-1 and -2 isoenzymes. *Int J Biochem Cell Biol* 1999; **31**: 551–557.
2. Hsu AL, Ching TT, Wang DS, *et al*. The cyclooxygenase- 2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2. *J Biol Chem* 2000; **275**: 11397–11403.
3. Smith WL, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular, and molecular biology. *Annu Rev Biochem* 2000; **69**: 145–182.
4. Boland GP, Butt IS, Prasad R, Knox WF, Bundred NJ. COX-2 expression is associated with an aggressive phenotype in ductal carcinoma *in situ*. *Br J Cancer* 2004; **90**: 423–429.
5. Gasparini G, Longo R, Sarmiento R, Morabito A. Inhibitors of cyclo-oxygenase 2: a new class of anticancer agents? *Lancet Oncol* 2003; **4**: 605–615.
6. Chang SH, Liu CH, Conway R, *et al*. Role of prostaglandinE2-dependent angiogenic switch in cyclooxygenase 2- induced breast cancer progression. *Proc Natl Acad Sci USA* 2004; **101**: 591–596.
7. Kirkpatrick K, Ogunkolade W, Elkak AE, *et al*. The association between cyclooxygenase-2 expression and cell proliferation and angiogenesis in human breast cancer. *Breast Cancer Res* 2001; **3**: A37.
8. O'Neill GP, Ford-Hutchinson AW. Expression of mRNA for cyclooxygenase-1 and cyclooxygenase-2 in human tissues. *FEBS Lett* 1993; **330**: 156–160.
9. Ristimaki A, Sivula A, Lundin J, *et al*. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. *Cancer Res* 2002; **62**: 632–635.
10. Barnes NL, Boland GP, Cramer A, Knox WF, Bunderd NJ. Recurrence of ductal carcinoma *in situ*: the role of COX-2 expression. *Br J Surg* 2004; **91**(S1): 37
11. Hawkey CJ. COX-2 inhibitors. *Lancet* 1999; **353**: 307–314.
12. Harris RE, Chlebowski RT, Jackson RD, *et al*. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. *Cancer Res* 2003; **63**: 6096–6101
13. Giardiello FM, Hamilton SR, Krush AJ, *et al*. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993; **328**: 1313–1316.
14. Gately C, Miers M, Mansel R E, Hughes Le. Drug treatment for Mastalgia:17 year experience in Cardiff Mastalgia Clinic. J Royal Soc Med1992;85:12.



PARAMETER	EPO (n= 1918) (%)	COX (n= 1918) (%)
NO REDUCTION	50	20
REDUCTION < 1CM	40	50
REDUCTION > 1CM	10	30

Table 1: Effect of EPO & COX-2 inhibitors in Lump size reduction

Cardiff Breast pain Score	EPO (%)	COX-2 (%)
CBS I	10	50
CBS II	30	30
CBS III	20	12
CBS IV	40	8

Table 2: Effect of EPO & COX-2 inhibitors in PAIN reduction