Augmentation of oral submucous fibrosis by NSAIDs in the presence of risk factors

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Abstract: Various Risk factors initiate Submucous fibrosis which may be augmented by NSAIDs. A number of animal studies on their mechanism indirectly support it especially regarding alterations in prostaglandin synthesis. This study has been designed to find association of these drugs with Oral Submucous fibrosis in the presence of risk factors. Newly diagnosed patients of Oral Sub mucous fibrosis were recruited for this study who attended Dental Department of Karachi Medical and Dental College from July 1 till Dec 31,2013.A structured interview and medical record of each patient was used to determine the demographic profile, any addiction, previous and present illnesses and drug (s) used. Through examination of Oral cavity was carried out to access the severity of disease as per modified Khanna & Andrade Classification (1995). Statistical Analysis was done by SPSS 15. Total 102 patients were recruited from dental OPD as per criteria of inclusion. Among these patients 36 (49.31%) were using NSAIDs in which Acetaminophen (30.55%), Acetylsalicylic acid (25.00%) and Diclophenac (19.44%) were 1st, 2nd and 3rd most common drugs. Data shows that 14 patients (28.88%) had mild and 22(61.11%) had sever fibrosis which was significantly high ($P<0.05$). Mild fibrosis was seen in 05 (45.46%) and Sever fibrosis in 06 (54.54%) out of total 11 patients who were using NSAIDSs since less than or equal to 6 months. Similarly mild fibrosis was seen in 09 (36.00%) and Sever fibrosis in 16 (64.00%) out of total 25 patients who were on NSAIDs since more than 6 months. No statistical significant difference ($P>0.05$) in severity of fibrosis is seen in patients who were using NSAIDs since less than or equal to 6 months but statistical significant difference ($P<0.05$) in severity of fibrosis is seen in patients who on these drugs since more than 6 months. Addiction burden was calculated by Average Duration x Average Frequency, which was 92.72 for Pan, 88.88 for Supari and 61.30 for Miscellaneous. No statistically significant difference ($P>0.05$) was seen in addiction burden of various substances in these patients. An association of NSAIDs with Oral Sub mucous fibrosis exists. The pathology is augmented if these drugs are used in the presence of risk factors. Therefore these drugs should not be prescribed to these patients until a clear benefit is not targeted.

Keywords: Oral Submucous fibrosis, NSAID, pre-malignant changes.

INTRODUCTION

A chronic progressive precancerous condition of the oral mucosa or Oral Submucous fibrosis (OSF) is characterized by burning sensation and irreversible fibrosis leading to difficulty in opening the mouth, speech and swallowing. The strongest risk factor is the chewing of betel quid containing areca nut, which is highly prevalent in India and South-East Asia (Murti *et al* 1995, Gupta and Ray 2004). In such patients, oral epithelium becomes atrophic and more prone to the effects of carcinogens.

Betel quid is a combination of the areca nut, betel leaf, tobacco, slaked lime (calcium hydroxide), and catechu (Cox and Walker 1996). Betel nuts contain many products believed to effect fibroblasts, for instance, arecoline, safrole, flavonoid and affects gene expression in fibroblasts, ultimately leading to OSF (Canniff and Harvey 1981; Harvey *et al* 1986; van Wyk *et al* 1993).

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Non-steroidal anti-inflammatory drugs are aspirin like drugs with anti-inflammatory, anti-pyretic and analgesic properties. Anti-inflammatory action occurs by the inhibition of cyclooxygenase (Vane and Botting 1998), the enzyme responsible for the biosynthesis of the prostaglandin and certain autacoids. Prostaglandin is believed to block fibroblast proliferation (Kohyama *et al* 2001) and since NSAIDs decrease prostaglandin, these drugs might play a role in increasing fibrosis in OSF patients. So, in this research, we have studied the association of NSAIDs in the development of Oral sub mucous fibrosis.

MATERIALS AND METHODS

This study was conducted in the Dental Surgery OPD of Karachi Medical and Dental College from July 1 till Dec 31, 2013 after approval of Institutional Ethical Committee.

138 patients attended the OPD with various complaints related to Oral Cavity. A total 102 patients were diagnosed

to have oral sub mucous fibrosis. Among them 73 were recruited for this cross-sectional study who were using some medication (from only one group of drugs) since more than 3 months and had habit of Pan, Sapari or any other chewable abused substance (other than Chewing gum) since more than 1 year. A structured interview was taken after consent of each patient. His/her medical record was obtained. Demographic profile, detail of addiction, present and past illnesses and drug(s) used were noted.

A detailed examination of their oral cavity for assessing the severity of disease was carried out. They were divided into patients with Mild to moderate and Sever Submucous fibrosis using Khanna and Andrade (1995) Criteria as.

1) Mild to Moderate Fibrosis that contained Group I and II patients of this criteria and defined as early stage patients with an interincisal distance of greater than 26 mm.
2) Sever Fibrosis that contained Group III and IV patients of this criteria and defined as moderately advanced cases with an interincisal distance less than 26 mm. with fibrotic bands at the soft palate, and pterygomandibular raphe and anterior pillars of fauces or with sever trismus and extensive fibrosis of all the oral mucosa or with premalignant and malignant changes throughout the mucosa.

Addiction burden was simply calculated by multiplication of Average duration and Average frequency for substance abused.

Statistical analysis was performed using SPSS version 15 for windows. Data was expressed as MEAN ±SE for continuous variables. Student t test and Multiple ANOVA were used to compare two and multiple parameters respectively.

RESULTS

Table 1 shows the characteristics of 102 patients who were newly diagnosed to have sub mucous fibrosis.

Table 2 reveals the number and percentage of patients who were taking different medicines and had habit of Pan, Supari or some Chewable substance. Among 73 patients, 36(49.31%) patients were taking NSAIDs, 13 (17.80%) Antihypertensive and 24 (32.87%) Miscellaneous drugs.

Table 3 shows the different NSAIDs used by the patients. Acetaminophen was used by 11 (30.55%) patients, Acetylsalicylic acid by 09 (25.00%) patients and Diclophenac by 07 (19.44%) patients and these three drugs were considered as 1st, 2nd and 3rd most common drugs.

Table 4 represents division of patients according to drug use. Data shows 14 patients (28.88%) had mild and 22 (61.11%) had sever fibrosis among 36 patients who were using NSAIDS. Sever fibrosis was significantly high ($P<0.05$) in this group. Similarly 8 patients (61.53%) had mild and 05(38.46%) had sever fibrosis among 13 patients who were using Antihypertensives. The difference between these two groups was not statistically significant ($P>0.05$). Miscellaneous drug user group of patients contained 14 patients (58.33%) with mild and 10 patients (41.66%) with sever fibrosis among 24 patients. The difference between these two groups was not statistically significant ($P>0.05$).

Table 5 depicts the duration of NSAIDs use in 36 patients. This group contains 25 patients (69.44%) who were using NSAIDs since more than 6 months and 11 patients (30.55%) who were using these drugs for less than 6 months. No statistical significant difference ($P>0.05$) is seen between these groups.

Table 6 shows severity of disease in 36 patients of Submucous fibrosis according to duration of NSAIDs use. Mild fibrosis was seen in 05 (45.46%) and Sever fibrosis in 6 (54.54%) out of total 11 patients who were using NSAIDs since less than or equal to 6 months. Similarly mild fibrosis was seen in 09 (36.00%) and Sever fibrosis in 16 (64.00%) out of total 25 patients who were on NSAIDs since more than 6 months. No statistical significant difference ($P>0.05$) in severity of fibrosis is seen in patients who were using NSAIDs since less than or equal to 6 months but statistical significant difference ($P<0.05$) in severity of fibrosis is seen in patients who on these drugs since more than 6 months.

Table 7 shows addiction burden in the patients, which was 92.72 for Pan, 88 for Supari and 61.30 others. No statistically significant difference ($P>0.05$) was seen in different groups.

DISCUSSION

Risk factors like areca nut has well established role in OSF (Murti *et al* 1995, Gupta and Ray 2004) but our study shows an augmentation of this pathology by NSAIDs in the presence of these risk factors. This requires an immediate attention by Clinicians involved in the treatment of OSF patients because NSAIDs are prescribed commonly to these patients to reduce the pain. Although further support to this association requires a large multicenter clinical study but ample support has been extracted from basic research to establish the role of NSAIDs in OSF.

Table 1: Characteristics of 102 patients.

Mean Age ± SE (Range) in Years	51.32±19.12(31-72)
Sex	58 males and 44 females
Addiction	76 (74.51%) Pan and Supari Both
	19(18.62%) Pan only
	04(03.92%) Supari only
	03 (02.94%) Misc.
Duration of Addiction ± SE (Range) in years	13.32±05.12(08-19)

Non-steroidal anti-inflammatory drugs work by inhibition of the enzyme cyclooxygenase (Vane and Botting 1998) responsible for the biosynthesis of prostaglandins, which have various functions and also affect fibroblasts. A metabolite, PGE_2 inhibits fibroblast proliferation and collagen production, is important in normal healing (Kohyama 2001). Similarly another metabolite, PGI_2 stops the activation of fibroblast (Stratton and Shiwen 2010). Increased fibro proliferation takes place in alveolar epithelial cells in diminished production of prostaglandins (Moore 2003). Therefore, NSAIDs enhances the activity of fibroblast by inhibition of prostaglandin. This supports augmentation of OSF by NSAIDs.

Table 2: Drug use in 73 newly diagnosed patients of Submucous fibrosis.

Drugs	No. of patients	Percentage
NSAIDs	36	49.31%
Antihypertensives	13	17.80%
Miscellaneous	24	32.87%

Table 3: Different NSAIDs used by the patients.

Drugs	No. of patients	Percentage
Acetaminophen	11	30.55%
Acetylsalicylic acid	09	25.00%
Diclofenac	07	19.44%
Ibuprofen	05	13.88%
Miscellaneous	04	11.11%

No study has indicated NSAIDs among risk factors for the development of OSF. Therefore we believe that NSAIDs only increases the rate of fibrosis by augmenting the effect of risk factors of OSF. Areca nut is an important established risk factor of OSF. All patients in our study were habitual user of areca nut (Addiction burden 92.72 for Pan, 88 for Supari and 61.30 others in our patients), containing substances that irritate the oral mucosa, making it lose its elasticity. Arecoline, an active alkaloid, which is present in betel nuts, stimulates fibroblasts to increase production of collagen by 150% (Canniff and Harvey 1981). It also inhibits metalloproteinases (particularly metalloproteinase-2) (Chang 2002), thus decreasing the overall breakdown of tissue collagen. Moreover, inhibition of gelatinase A activity and stimulation of tissue inhibitor of metalloproteinase-1 (TIMP-1) by arecoline leads to the accumulation of the components of extracellular matrix (Moore 2003). It is also believed that arecoline and safrole increase the mRNA expression of tissue inhibitor of metalloproteinases (TIMPs), decreasing collagen degradation (Shieh 2003). NSAIDs augment this effect of areca nut, as evidenced by an increase number of OSF patients (especially sever fibrosis) in our study who took NSAIDs (P=0.042

for NSAIDs but P=0.0194 for Antihypertensives and P=0.271 for other drugs for the patients with severe fibrosis as compared to mild fibrosis). Similarly it is supported by the fact that OSF was sever in patients who were using NSAIDs for a longer period (P=0.108 in patients who were using NSAIDs for less than or equal to 6 months as compared to P=0.048 in patients who were using NSAIDs for more than 6 months if severity of fibrosis is compared). A study held in 2002 stated that NSAIDs inhibit matrix metalloproteinase-2 (Mei-Ren Pan and Wen-Chun Hung 2002). This shows an enhanced suppression of matrix metalloproteins responsible for degrading collagen, thereby increasing the amount of collagen in a tissue with prolong duration of these drugs. To further support our result, a study published in 2010 argued the link of NSAIDs with hypertrophic scar formation, an aberrant form of wound healing (Aarabi *et al* 2007) that indicates an exaggerated function of fibroblasts and excess accumulation of extra cellular matrix during wound healing, associated with overproduction of TGF-β and suppression of PGE_2 (Sui *et al* 2010). Since, areca nut continuously damages the oral mucosa, healing in the presence of NSAIDs can increase fibroblasts activity.

Role of NSAIDs as a risk factor cannot be ruled out completely. This is not a part of our study so our data does not discuss this fact. However enough indirect evidences support it. In OSF, NF-kappa B expression is elevated in buccal mucosal fibroblast and its expression is also activated by areca quid chewing (NiWF *et al* 2007). On the other hand, Aspirin is also believed to activate the NF-kappa B signaling pathway and induces apoptosis in intestinal neoplasia (Strak *et al* 2007). If the same effect is produced in fibroblasts of oral cavity, then these studies might suggest the role of NSAIDs in causing fibrosis in OSF patients. A study held in 2010 suggested that chronic

Table 4: Drug use and severity of sub mucous fibrosis in 73 patients (as per Khanna & andrade classification)

Drugs	Mild Fibrosis (Group I & II)	Sever fibrosis (Group III & IV)	Significance
NSAIDs	14/36(28.88)*	22/36(61.11)	P=0.039
Antihypertensives	08/13(61.53)	5/13(38.46)	P=0.195
Miscellaneous Drugs	14/24(58.33)	10/24(41.66)	P=0.207

Table 5: Duration of NSAIDs use in patients of sub mucous fibrosis

Duration of drug use	No. of patients	Percentage	Significance
More than 6 months	25	69.44%	P=0.057
Less than 6 months	11	30.55%	

Table 6: Severity of fibrosis in 36 patients of sub mucous fibrosis according to NSAIDs use. (as per Khanna & Andrade Classification)

Duration of NSAIDs use	Mild Fibrosis (Group I & II)	Sever fibrosis (Group III & IV)	Significance
Less than or equal to 6 months	05/11(45.46%)*	06/11 (54.54%)	P=0.108
More than 6 months	09/25(36.00%)	16/25 (64.00%)	P=0.048

*(Number of Patients /Total number of Patients)

Table 7: Addiction pattern in 36 patients using NSAIDs

Habit	Average Duration (years)	Average Frequency (packets per day)	Addiction Burden (Avg. Duration x Avg. Freq.)
Pan	12.2	7.6	92.72
Supari*	7.25	12.25	88.88
Others	8	7.67	61.3

P=0.544 and 0.398 if Pan is compared with Supari and Others respectively. *Supari is sweet betel nuts

celecoxib (selective COX-2 inhibitor) use promotes myofibroblast-associated intestinal fibrosis (Davids 2010). If effect is assumed to be the same on oral fibroblasts, then link with duration of use remains uncertain.

Association of antihypertensives in the development of OSF is not supported by literature but it can not be ignored completely because it is established firmly that many angiogenic factors are involved in activation of endothelial cells (Agarwal 2014) which are responsible for submucus fibrosis and tumor growth and are affected by antihypertensive therapy (Ferroni 2012).

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