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ORIGINAL ARTICLE

Prevalence, Risk Factors, Awareness, and Response to Pharmacological Treatment of Oral Potentially Malignant Disorders and Gutka Dependence among Gutka Users in Karachi: A Mixed-Method Interventional Study

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ABSTRACT

Background: Oral potentially malignant disorders (OPMDs), including Oral Submucous Fibrosis (OSMF) and leukoplakia, represent major clinical challenges in South Asia. In Karachi, Pakistan, the widespread consumption of gutka smokeless tobacco product containing areca nut, drives high rates of OPMDs and chemical dependence. This study evaluated the prevalence, risk factors, baseline awareness, and response to combined pharmacological therapy alongside addiction cessation counselling among habitual gutka users in Karachi.

Methodology: A mixed-method interventional study was conducted over a 12-month period involving 280 habitual gutka users. Quantitative evaluation assessed baseline demographic data, gutka dependence severity (using a modified Fagerström Test for Nicotine Dependence adapted for smokeless tobacco), clinical OPMD prevalence, and pre/post-intervention mouth opening (interincisal distance in mm). Qualitative data were gathered via focus group discussions to explore socio-cultural drivers of addiction. Participants diagnosed with OPMDs received a 12-week standardized pharmacological regimen consisting of oral lycopene systemic alpha-lipoic acid, intralesional triamcinolone acetonide (10 mg/mL) plus hyaluronidase (1500 IU) for advanced trismus, alongside nicotine replacement therapy (NRT gum) and behavioral cessation support. Outcomes were evaluated using paired ttt-tests and Chi-square analysis ($p<0.05$).

Results: The overall prevalence of clinically confirmed OPMDs among enrolled gutka users was 64.3% (n=180), with OSMF accounting for 48.6% (n=136) and leukoplakia 15.7% (n=44). High daily frequency (>5 packets/day}, OR=4.25,$p<0.001$ and long duration of use >5 years, OR=5.12,$p<0.001$ were key independent risk factors. Baseline awareness regarding the malignant transformation risk of OPMDs was low (31.4%). Following 12 weeks of pharmacological intervention and NRT support, 58.3% (n=105n = 105n=105) achieved successful gutka cessation. Pharmacological therapy resulted in a significant improvement in mean interincisal distance (21.4±4.2 mm to 31.8±4.6 mm, $p<0.001$) and a 74.5% reduction in burning mucosal sensation scores.

Conclusion: Gutka dependence in Karachi is associated with a high prevalence of OPMDs, driven by low community awareness and intense chemical addiction. Combined pharmacological management pairing systemic antioxidants and anti-fibrotic therapies with structured NRT and behavioural cessation support effectively reduces lesion severity, improves mouth opening, and facilitates gutka cessation.

Keywords: Oral Potentially Malignant Disorders; Gutka Dependence; Oral Submucous Fibrosis; Pharmacotherapy; Nicotine Replacement Therapy; Lycopene; Karachi.

INTRODUCTION

Oral cancer represents the second most common malignancy in Pakistan and the leading cancer among males in urban coastal centers such as Karachi[1]. This alarming epidemiological footprint is driven by the widespread consumption of smokeless tobacco products, most notably gutka. Gutka is a commercially packaged, highly addictive mixture composed of crushed areca nut (Areca catechu), dried tobacco, slaked lime (calcium hydroxide), catechu, and proprietary chemical flavoring agents. The synergy between areca nut alkaloids (primarily arecoline and arecaidine) and tobacco-specific nitrosamines (TSNAs, such as N'-nitrosonornicotine [NNN] and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]) creates a potent carcinogenic and fibrogenic mucosal environment[2,3].

Chronic exposure to gutka induces Oral Potentially Malignant Disorders (OPMDs), a heterogeneous group of mucosal lesions comprising Oral Submucous Fibrosis (OSMF), oral leukoplakia, erythroplakia, and oral lichenoid reactions[4]. OSMF is characterized by chronic inflammation, localized oxidative stress, progressive submucosal collagen deposition, and vascular constriction, culminating in progressive trismus, mucosal burning, and severe anatomical deformity[5]. The rate of malignant transformation of OSMF to oral squamous cell carcinoma (OSCC) ranges between 4.5% and 7.6%. Despite legislative bans on the manufacture and sale of gutka in Sindh, informal production and low market costs perpetuate high rates of daily consumption across diverse socio-economic strata in Karachi[6].

From a pharmacological perspective, managing gutka-induced OPMDs presents a dual challenge: halting progressive mucosal fibrogenesis while addressing severe physical and psychological chemical dependence[7]. Arecoline acts as a muscarinic receptor agonist, stimulating fibroblast proliferation and upregulating transforming growth factor-beta 1 (TGF-β1\beta1β1) expression, while slaked lime facilitates rapid nicotine mucosal absorption, causing physical addiction[8]. Pharmacological strategies targeting early OPMDs involve systemic antioxidants (such as lycopene and alpha-lipoic acid) to neutralize reactive oxygen species (ROS), along with intralesional corticosteroids and hyaluronidase to breakdown fibrous bands. However, pharmacological mucosal therapies often fail if active gutka consumption persists[9]. Therefore, integrating nicotine replacement therapy (NRT) and structured addiction counseling with targeted pharmacotherapy is essential. This mixed-method interventional study was conducted to determine the prevalence, risk factors, baseline awareness, and clinical response to combined pharmacological treatment and cessation counseling among gutka users in Karachi.

METHODOLOGY

This study utilized a mixed-method interventional design combining a quantitative clinical trial with qualitative Focus Group Discussions

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(FGDs). The study was conducted at tertiary care dental hospitals and outpatient oral medicine centers in Karachi over a 12-month period, from July 2022 to June 2023. A total of 280 habitual gutka users were recruited through non-probability sampling. Inclusion Criteria: Adult participants (aged 18–60 years) with a history of daily gutka consumption for ≥1 year, willing to undergo clinical examination and participate in a 12-week cessation and pharmacological trial. Exclusion Criteria: Patients with established oral squamous cell carcinoma (OSCC) at baseline, active systemic autoimmune disorders, pregnancy, prior surgical management for OSMF, or known hypersensitivity to trial medications

Quantitative Assessment and Baseline Screening: Data were gathered using a validated questionnaire capturing demographic parameters, daily packet frequency, duration of habit, and awareness regarding oral cancer risks. Gutka dependence was quantified using a modified Fagerström Test for Nicotine Dependence adapted for Smokeless Tobacco (FTND-ST). Clinical examination identified and categorized OPMDs based on World Health Organization (WHO) diagnostic criteria. Clinico-anatomical severity of OSMF was staged (I–IV) via maximum interincisal distance (IID in mm) measured with a calibrated digital Vernier caliper, alongside subjective mucosal burning sensation evaluated using a 0–10 Visual Analog Scale (VAS).

Pharmacological and Cessation Interventions: Participants diagnosed with OPMDs (n=180) were enrolled in a 12-week combined therapeutic protocol. Oral Lycopene capsules (16 mg/day) combined with Alpha-Lipoic Acid (300 mg/day) administered daily for 12 weeks to suppress ROS-mediated fibrogenesis. Patients with Stage II–IV OSMF (IID <30 mm) received bi-weekly intralesional injections of Triamcinolone Acetonide (10 mg/mL) plus Hyaluronidase (1500) dissolved in 0.5 mL of 2% lignocaine, injected bilaterally into the buccal mucosa for 6 weeks. To manage gutka withdrawal, participants received NRT gum (2 mg based on FTND-ST dependence score) alongside weekly structured behavioural counselling sessions focused on habit substitution and trigger management.

Qualitative Component: Four focus group discussions (n=8–10 participants per session were conducted to explore socio-cultural drivers of gutka initiation, peer influences, perceived barriers to quitting, and community misconceptions regarding smokeless tobacco risks.

Statistical Analysis: Quantitative data were analyzed using SPSS Version 26.0. Continuous variables (IID in mm, VAS scores) were expressed as mean ± standard deviation (SD) and compared pre- and post-intervention using paired Student's t-tests. Categorical variables were evaluated using Chi-square tests and multivariable logistic regression to identify independent risk factors for OPMD development. A two-tailed p-value <0.05 was considered statistically significant. Qualitative transcripts were analyzed using thematic analysis.

RESULTS

Baseline Demographics and OPMD Prevalence: Among the 280 gutka users evaluated, 82.1% (n=230) were male and 17.9% (n=50) were female, with a mean age of 32.4±7.8 years. Clinical screening identified OPMDs in 64.3% (n=180) of the total population. Oral Submucous Fibrosis (OSMF) was the most prevalent condition (48.6%, n=136), followed by leukoplakia (15.7%, n=44). High gutka dependence (FTND-ST score ≥7) was documented in 57.1% (n=160) of participants.

Table 1: Baseline Demographics and Prevalence of OPMDs (N=280)

Variable	Total Cohort (N=280)	OPMD Present (n=180)	OPMD Absent (n=100)	p-value
Mean Age ± SD (years)	32.4 ± 7.8	34.2 ± 8.1	29.1 ± 6.4	<0.001*
Gender, n (%)				0.042*
* Male	230 (82.1%)	154 (85.6%)	76 (76.0%)	
* Female	50 (17.9%)	26 (14.4%)	24 (24.0%)	
Daily Packet Usage, n (%)				<0.001*
* 1−4 packets/day	112 (40.0%)	48 (26.7%)	64 (64.0%)	
* ≥5 packets/day	168 (60.0%)	132 (73.3%)	36 (36.0%)	
Duration of Use, n (%)				<0.001*
* <5 years	94 (33.6%)	30 (16.7%)	64 (64.0%)	
* ≥5 years	186 (66.4%)	150 (83.3%)	36 (36.0%)	
Specific OPMD Diagnosis, n (%)				
* Oral Submucous Fibrosis (OSMF)	136 (48.6%)	136 (75.6%)		
* Oral Leukoplakia	44 (15.7%)	44 (24.4%)		

Table 2: Pre- and Post-Intervention Outcomes in OPMD Patients (n=180n = 180n=180)

Clinical Outcome Parameter	Baseline (Week 0)	Post-Treatment (Week 12)	Mean Difference (95% CI)	p-value
Interincisal Distance (mm, Mean ± SD)	21.4 ± 4.2	31.8 ± 4.6	+10.4 (9.2 – 11.6)	<0.001*
Mucosal Burning VAS Score (0–10)	7.6 ± 1.4	1.9 ± 0.8	-5.7 (-6.1 – -5.3)	<0.001*
Successful Gutka Abstinence, n (%)	0 (0.0%)	105 (58.3%)		<0.001*

Multivariable Risk Factor and Awareness Analysis: Multivariable logistic regression identified consuming ≥5 packets of gutka per day (a OR=4.25, 95% CI: 2.41–7.48, p<0.001) and chewing duration ≥5 years (OR=5.12, 95% CI: 2.85–9.20, p<0.001) as primary independent predictors of OPMD development. Baseline awareness regarding the pre-cancerous nature of gutka-induced lesions was poor: only 31.4% (n=88) recognized that gutka causes mouth-opening loss, and 24.6% (n=69) were aware of its link to oral carcinoma.

Post-Intervention Clinical and Pharmacological Outcomes: Following the 12-week combined intervention protocol (antioxidants, intralesional anti-fibrotics, NRT, and counseling), 58.3% (n=105) of OPMD patients successfully achieved complete gutka abstinence. Patients undergoing pharmacological treatment exhibited significant clinical improvements:

- **Interincisal Distance (IID):** Mean mouth opening increased significantly from 21.4±4.2 mm at baseline to 31.8±4.6 mm 12 weeks (p<0.001).
- **Mucosal Burning Sensation:** Mean VAS score for mucosal burning decreased by 74.5%, from 7.6 ± 1.47. at baseline to 1.9 ± 0.81 post-treatment (p<0.001).

Qualitative Findings: Thematic analysis of focus group discussions revealed three primary themes: (1) Ease of Accessibility and Low Cost gutka is easily accessible and cheaper than cigarette tobacco; (2) Peer Influence and Occupational Stress Reliever widespread use among manual laborers to alleviate fatigue; and (3) Lack of Quitting Support most users reported prior failed quit attempts due to severe nicotine withdrawal symptoms and a lack of access to NRT products.

DISCUSSION

The findings of this mixed-method interventional study highlight a major public health crisis in Karachi, where gutka dependence directly drives a high prevalence of Oral Potentially Malignant Disorders (64.3%). Oral Submucous Fibrosis represented the vast majority of identified lesions (48.6%), confirming that areca nut-

containing products pose a severe threat to oral mucosal health in urban Pakistani populations. The pathophysiological cascade of gutka toxicity is driven by the synergistic actions of its chemical constituents. Arecoline stimulates collagen synthesis in mucosal fibroblasts while downregulating matrix metalloproteinase-1 (MMP-1), causing insoluble collagen accumulation[10,11]. Concurrently, slaked lime induces local epithelial abrasion, facilitating deeper penetration of tobacco-specific nitrosamines (TSNAs) and generating high levels of intracellular reactive oxygen species (ROS)[12]. Our findings demonstrate that high daily consumption (≥5 packets/day) and long duration (≥5 years) significantly increase OPMD risk, reflecting a dose- and time-dependent toxic burden. A critical barrier identified in this study is the low baseline community awareness regarding OPMDs[13]. Less than one-third of participants understood that early symptoms, such as burning sensation and restricted mouth opening, are precursors to malignant oral carcinoma. Qualitative insights revealed that gutka is widely misperceived as a harmless habit or digestive aid, facilitating early habit initiation among young adults and manual laborers[14].

Crucially, our study demonstrates that combined pharmacological and addiction-focused interventions yield superior clinical outcomes compared to isolated mucosal treatments[15]. Systemic lycopene and alpha-lipoic acid act as potent ROS scavengers, downregulating pro-inflammatory cytokine cascades and inhibiting TGF-β1-driven collagen production[16],[17]. Bi-weekly intralesional injections of triamcinolone acetonide and hyaluronidase directly target mature submucosa: triamcinolone suppresses local inflammation, while hyaluronidase enzymatically cleaves hyaluronic acid matrix components, softening fibrous bands[18]. This dual approach achieved a statistically significant 10.4 mm average increase in interincisal distance and a 74.5% reduction in mucosal burning.

However, the sustained efficacy of pharmacological management relies on achieving long-term habit cessation. Gutka dependence is driven by rapid nicotine absorption facilitated by the alkaline pH of slaked lime[19,20]. By incorporating Nicotine Replacement Therapy (NRT) gum alongside structured behavioural counselling, 58.3% of participants achieved complete gutka abstinence at 12 weeks. Addressing nicotine withdrawal symptoms removed the primary driver of relapse, allowing the oral mucosa to heal under pharmacological support[21,22]. Limitations of this study include the 12-week intervention follow-up window; long-term longitudinal tracking over 1–3 years is needed to evaluate recurrence rates and long-term malignant transformation risk. Furthermore, expanding trial sites across rural Sindh would enhance the generalizability of these findings.

CONCLUSION

Gutka usage in Karachi is strongly associated with a high prevalence of Oral Potentially Malignant Disorders, particularly Oral Submucous Fibrosis, driven by high daily consumption, long habit duration, and low community health literacy. Combined interventional management pairing systemic antioxidants and intralesional anti-fibrotics with nicotine replacement therapy and behavioural cessation support effectively reduces mucosal burning, improves interincisal mouth opening, and facilitates high rates of habit cessation.

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