ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 19(13): 1377-1382 (2023)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

OPEN ACCESS GOLD

BIOMEDICAL INFORMATICS

www.bioinformation.net
Volume 19(13)

Research Article

Received December 1, 2023; Revised December 31, 2023; Accepted December 31, 2023, Published December 31, 2023

DOI: 10.6026/973206300191377

BIOINFORMATION Impact Factor (2023 release) is 1.9 with 2,198 citations from 2020 to 2022 across continents taken for IF calculations.

Declaration on Publication Ethics:
The author's state that they adhere with COPE guidelines on publishing ethics as described elsewhere at https://publicationethics.org/. The authors also undertake that they are not associated with any other third party (governmental or non-governmental agencies) linking with any form of unethical issues connecting to this publication. The authors also declare that they are not withholding any information that is misleading to the publisher in regard to this article.

Declaration on official E-mail:
The corresponding author declares that lifetime official e-mail from their institution is not available for all authors

Comments from readers:
Articles published in BIOINFORMATION are open for relevant post publication comments and criticisms, which will be published immediately linking to the original article without open access charges. Comments should be concise, coherent and critical in less than 1000 words.

Special Issue on Dental Biology
Edited by Vini Mehta & Hiroj Bagde
E-mail: vini.mehta@dpu.edu.in & vinip.mehta@gmail.com

Citation: Pandey *et al.* Bioinformation 19(13): 1377-1382 (2023)

Cryotherapy for oral potentially malignant disorders

Ashutosh Pandey[1], Sukirat Kaur[2], Albert Ashem[3], Shivangni Sarin[4], Rakesh Kumar Sahu[5], Braina P. Jadav[6], Dhaval Niranjan Mehta[7] & Ramanpal Singh Makkad[8*]

[1]Department of Dentistry, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India; [2]Department of Public Health Dentistry, Genesis Institute of Dental Sciences and Research, Ferozepur, India; [3]Department of Oral Medicine and Radiology, Dental College, RIMS, Imphal, Manipur, India; [4]Department of Oral & Maxillofacial Surgery, Army College of Dental Sciences, Secunderabad,

India; [5]Department of Oral Medicine and Radiology, New Horizon Dental College and Research Institute Sakri, Bilaspur, Chhattisgarh, India; [6]Department of Oral Medicine and Radiology, Ahmedabad, India; [7]Department of Oral Medicine and Radiology, Narsinbhai Patel Dental college and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India; [8]Department of Oral medicine and Radiology, New Horizon Dental College and Research, Institute, Sakri, Bilaspur, Chhattisgarh, India; *Corresponding author

Affiliation URL:
https://anmmc.ac.in/
https://www.gidsr.com/
https://www.rims.edu.in/secure/
https://www.acds.co.in/
https://www.nhdcri.in/
https://npdch.edu.in

Author contacts:
Ashutosh Pandey – E-mail: ashupandey289@gmail.com; Phone: +91 7644819363
Sukirat Kaur - E-mail: sukiratkor24@gmail.com; Phone: +91 7500968848
Albert Ashem - E-mail: albertashem@ymail.com; Phone: +91 9776589189
Shivangni Sarin - E-mail: shivangnisarin95@gmail.com; Phone: +91 8319201710
Rakesh Sahu - E-mail: bky.sahu1994@gmail.com; Phone: +91 8770692125
Braina P. Jadav - E-mail: drbrains97@gmail.com; Phone: +91 8866822957
Dhaval Niranjan Mehta - E-mail: drdhaval80@gmail.com; Phone: +91 98255 28915
Ramanpal singh - E-mail: drramanpal@gmail.com; Phone: +91 9098699300

Abstract:
Four surgical treatment modalities namely cryosurgery, scalpel and blade surgery, diode LASER surgery and CO_2 LASER surgery in the management of oral potentially malignant disorders (OPMDs) in terms of healing outcomes post operatively and recurrence is evaluated. The study included sixty outpatients whose biopsies revealed OPMDs (oral lichen planus, homogeneous leukoplakia, non-homogenous leukoplakia and erythroplakia). There is decrease in post-operative pain and oedema in all four treatment categories at one week follow up and two week follow up. It was observed that pain was low in cryosurgery treatment category at day of surgery as well as at one week of follow up as compared to diode LASER and CO_2 LASER. Observations from the study highlights that all four surgical modalities used in this study were effective for treatment of OPMDs, and the overall summation of the results of the study showed that cryotherapy seems to offer better clinically significant results than laser therapy.

Keywords: Cryosurgery, LASER, OPMDS

Background:
Cancer of oral cavity is one of the most serious issues of community-based health around the globe public health concern around the world **[1, 3].** One-third of the cases (37.5 percent) were found only in Asia. Scientists coined the phrase "premalignant lesion" to describe a disease that, if left untreated, could grow causing "cancer" **[4, 5].** Oral premalignant lesions (OPMLs), which affect about 3% of total human population, are a specific target for prevention of cancer of oral cavity **[6,7].** The importance of pre-cancer lesion like oral leukoplakia, oral erythroplakia, or oral erythro leukoplakia arises from the large number of patients where a biopsy reveals dysplasia or similar "frank cancer **[8-9].** There is a progressive histopathological sequence which can be graded as regular, hyperplastic as well as carcinoma in situ during the progression of premalignant lesion to the malignant lesion **[10, 11].** Oral pre-malignant lesions can be identified and managed with a visual inspection and are conveniently accessible for further testing including microscopy and biopsies **[12, 13].**Early diagnosis of abnormalities reduces mortality and morbidity, but prolonged identification, particularly in places with the highest incidence rate, lowers the chance of survival, despite modern treatment procedures **[14, 15].** Pre-cancerous lesions of the oral cavity include leukoplakia of oral cavity, erythroplakia of oral cavity, oral sub-mucous fibrosis, condition of actinic keratosis, condition of discoid lupus erythematosus, condition of lichen planus of oral cavity, and condition of reverse smokers, all of which are referred to as "potentially malignant illnesses (OPMDs) **[16,17].** It has been documented that around 13% of these abnormalities of oral cavity get transformed into cancer of oral cavity **[18, 19].** Elimination of contributing variables such as tobacco use, smoking, discontinuing betel quid, and reduced or complete abstinence from alcohol consumption is the initial step in managing OPMDs **[20, 21].** Total quitting smoking can have a significant impact on the prognosis. The severity of the lesion, especially its location, dimensions, and position, together with any accompanying dysplasia, will also determine the course of treatment **[22, 23].** Numerous medicinal and surgical therapy techniques are used to control OPMDs. Reversing or completely eliminating the alterations to the oral mucosa is the aim of OPMD treatment. The medical line of care for OPMD comprises topical as well as systemic medicines such as vitamin A and retinoid, lycopene, ketorolac, systemic beta-carotene, topical and systemic corticosteroids and local bleomycin, with

varying degrees of efficacy **[24, 25].** While retinoid, or vitamin A, has been utilized as a medical treatment, there is not much scientific data to support its efficacy in lowering the rate of cancer transformation and relapse **13-15].** Traditional surgery using scalpel and blade and LASER (Light Amplified Stimulate Emission of Radiation) surgery are among the surgical treatment techniques that have been recommended for the management of OPMDs **[16-17].** The location and size of the disease restrict conventional operations. A straightforward, secure, tried-and-true method of treating OPMDs and some benign and precancerous lesions of the oral cavity is cryosurgery. Compared to traditional surgery, lasers offer a multitude of advantages, including targeted excision, easy achievement of homeostasis, and less discomfort and oedema after operation **[18, 19].** Although cryotherapy is being successfully utilized in management of different medical surgery, but its use in management of OPMDS is still being a field of research. No study has compared cryotherapy with other surgical modalities for OPMDS namely conventional scalpel blade surgery and LASERs **[20-23].** Hence, four surgical treatment modalities namely cryosurgery, scalpel and blade surgery, diode LASER surgery and CO2 LASER surgery in management of oral potentially malignant disorders (OPMDs) in terms of healing outcomes post operatively and recurrence were evaluated.

Table 1: Distribution of study participants

	Treatment Modality	Number
Category 1	Conventional scalpel blade surgery	15
Category 2	Diode LASER	15
Category 3	Nitrous oxide Cryotherapy	15
Category 4	CO_2 LASER	15

Methods and Materials:

The study included sixty outpatients whose biopsies revealed OPMDs (oral lichen planus, homogeneous leukoplakia, non-homogenous leukoplakia, and erythroplakia). The benefits and drawbacks of surgery were discussed with research participants. Blood examinations were performed on the patients, comprising clotting times, complete hemograms, bleeding times and random blood sugar tests. Patients with current cancer and those with OPMDs that reduced in size after habit discontinuation were not included in the study. There were 20 women and 40 males in the study sample, having a mean age of 35.5 years. Sixty patients were divided into four categories at random, with fifteen patients in each category. All the groups received any of the four treatment modalities **(Table 1).** A questionnaire was used to assess each patient, gathering information about their prior medical history, surgical history, and dental histories. An intraoral as well as extraoral assessment was also conducted. 2% lignocaine was mixed with 180000 epinephrine was injected into the surgical site for each group as a local anesthetic. In category 1: A scalpel and 15 no blade was used to mark an incision at the circumference of lesion in the form of triangular incision with base at posterior border and apex at anterior portion of lesion. The lesion along with tissue was retracted with a tissue forceps and complete excision was carried out. It was followed by suturing. In category 2: Local anesthesia was applied while a 4 watt diode laser system operating at 970 nm was employed continuously. Utilising a surgical marker, the lesions were located and their boundaries noted. The lesion was totally ablated when the treatment was administered in contact mode. In category 3: A application directly of nitrous oxide cryoprobe with a temperature of -65 to -85 degrees Celsius was used to carry out the cryosurgery process. After the ice ball formed, the cryoprobe was administered for 45–60 seconds while the tissue was given time to fully thaw before the probe was reapplied. For a minimum of 2-3 freeze-thaw cycles, the cryoprobe was used. After applying the probe to neighbouring locations one after the other, a quick frozen area-filled spatial overlap was created. In category 4: Surgery was conducted using a 10.6 µm wavelength CO2 laser beam. The targeting beam was employed, with a typical spot size of 1 mm, and the power output was kept within the customary standard range of 5 to 15 watts on pulsed/continuous mode. The ablation was carried out in a non-contact mode by manoeuvring a slightly defocused point of CO2 laser over the lesion until full evaporation while it reached sub-mucosa. The area of tissue to be ablated was first marked with a margin of around 3mm in a pulsed mode. To cure extensive lesions, the mapping approach had to be applied multiple times. On the day of the procedure, the bleeding and pain levels of each patient in the four categories were evaluated. A visual analogue scale was used to assess pain, with 0 and 10 representing the extremes and representing "no pain" and "maximum pain imaginable," respectively. By noting whether spontaneous bleeding occurred or not, bleeding was evaluated. Evaluation of oedema consisted of comparing the region of the wound to the anatomical region of the contralateral side to see whether asymmetry existed. Infection, scar development, and slough were assessed solely by visual inspection. During the 1st and 2nd postoperative week, patients had follow-up appointments to monitor pain, oedema, slough development, and infection. Evaluations of the development of scars and lesion reappearance were conducted three months and six months after surgery. Infections or problems during and after surgery were later identified.

Statistical analysis:

The frequency distribution for each research parameter (categorical variable) that was to be compared between the four categories was given in terms of number and percentage. The distribution and association of the research variables among the four categories at each time interval were compared using the Chi-Square test. The pain scores' mean and standard deviation (SD) were calculated, and the one-way ANOVA test was used to compare the groups' scores. Tukey's HSD test was then used as a post hoc analysis. P<0.05 was used as the significance level (P-Value) threshold.

Table 2: Type of OPMDs

	No (n=60)	Percentage
Homogenous leukoplakia	20	33.33
Non homogenous leukoplakia	14	23.34
Oral lichen planus	18	30.00
Erythroplakia	08	13.33

Table 3: VAS score for post-operative pain (mean ± SD) in all four treatment modalities

	Day of surgery	One week follow up	Two week follow up
Scalpel blade surgery	2.9± 0.13	1.6±0.02	0.7±0.04
Diode LASER	2.1± 0.01	1.4±0.04	0.5±0.01
Cryotherapy	1.6± 0.34	1.1± 0.31	0.2± 0.02
CO_2 LASER	2.0± 0.12	1.5± 0.14	0.4± 0.03
P value	0.001*	0.0023*	0.67*

*indicates statistically significant difference.

Table 4: Incidence of oedema (%) in all four treatment modalities

	One week follow up	Two week follow up
Scalpel blade surgery	45%	03%
Diode LASER	38%	04%
Cryotherapy	25%	02%
CO_2 LASER	40 %	04%
P value	0.001*	0.89

*indicates statistically significant difference.

Table 5: Incidence of infection (%) in all four treatment modalities

	One week follow up	Two week follow up
Scalpel blade surgery	15%	00%
Diode LASER	18%	01%
Cryotherapy	15%	00%
CO_2 LASER	18 %	01%
P value	0.71	0.34

Table 6: Incidence of bleeding (%) in all four treatment modalities

	Day of surgery
Scalpel blade surgery	67%
Diode LASER	04%
Cryotherapy	02%
CO_2 LASER	03
P value	0.001*

*indicates statistically significant difference.

Table 7: Incidence of scar (%) in all four treatment modalities

	3 months	6 months
Scalpel blade surgery	14%	02%
Diode LASER	38%	18%
Cryotherapy	35%	15%
CO_2 LASER	38 %	18%
P value	0.001*	0.004*

*indicates statistically significant difference.

Table 8: Incidence of slough (%) in all four treatment modalities

	First week	Second week
Scalpel blade surgery	13%	03%
Diode LASER	36%	16%
Cryotherapy	37%	17%
CO_2 LASER	35 %	15%
P value	0.001*	0.004*

*indicates statistically significant difference.

Table 9: Incidence of recurrence (%) for all four treatments

	3 months	6 months
Scalpel blade surgery	12%	04%
Diode LASER	36%	16%
Cryotherapy	32%	12%
CO_2 LASER	31 %	11%
P value	0.001*	0.002*

*indicates statistically significant difference.

Results:

In this study, 20 cases of homogenous leukoplakia, 14 cases of non-homogenous leukoplakia, 18 cases of oral lichen planus and 8 cases of erythroplakia were included (**Table 2).** There is decrease in post-operative pain in all four treatment categories at one week follow up and two week follow up. It was observed that pain was low in cryosurgery treatment category at day of surgery as well as at one week of follow up as compared to diode LASER and CO_2 LASER. The findings were statistically significant (p=0.001). It was observed that post-operative pain at two weeks of follow up was comparable in all treatment modalities. VAS values for pain at day of surgery was 2.9± 0.13, 2.1± 0.01, 1.6± 0.34 and 2.0± 0.12 in scalpel-blade surgery, Diode LASER , cryotherapy and CO_2 LASER respectively. Similarly VAS values for pain at one week follow up was1.6±0.02, 1.4±0.04, 1.1± 0.31 and 1.5± 0.14 in scalpel - blade surgery, Diode LASER, cryotherapy and CO_2 LASER VAS scores. VAS values for pain at two week follow up was 0.7±0.04, 0.5±0.01, 0.2± 0.02 and 0.4± 0.03 in scalpel- blade surgery, Diode LASER, cryotherapy and CO_2 LASER **(Table 3).** There was maximum pain in scalpel blade surgery at day of surgery and one week follow up.

There was low proportion of patients with oedema in cryosurgery group as compared to Diode LASER, scalpel blade surgery and CO_2 LASER, at one week follow up. The findings were significant statistically (0.001). There was decrease in oedema in all treatment modalities at two week follow up. The proportion of oedema in at two week follow up in different treatment modalities was comparable with p = 0.89 **(Table 4).**

The proportion of patients with infection was comparable in cryosurgery category, diode LASER category , scalpel blade surgery and CO_2 LASER category one week follow up (p=0.71). There was decrease in infection in all treatment modalities at two week follow up. The proportion of infection in at two week follow up in different treatment modalities was comparable (p=0.34) **(Table 5).** The incidence of bleeding was maximum (67%) in scalpel blade surgery at day of surgery as compared to other treatment modalities. The findings were statistically significant (p=0.001). There was very low incidence of bleeding in cryotherapy category, DIODE LASER and CO_2 LASER and the incidence was comparable between cryotherapy category, DIODE LASER and CO_2 LASER **(Table 6).** The proportion of patients with scar at 3 months follow up and 6 months follow up was lower in scalpel blade surgery as compared to cryosurgery category, Diode LASER category, and CO_2 LASER category. The findings were significant statistically (p=0.001). There was decrease in scar in all treatment modalities at 6 month follow up. The proportion of scar at 6 month follow up in scalpel blade category was minimum as compared to cryosurgery category, Diode LASER category , and CO_2 LASER category (p=0.004). The incidence of scar in cryosurgery category, Diode LASER category and CO_2 LASER category was comparable at 3 months and 6 months follow up **(Table 7).** The proportion of patients with slough at first week follow up and second week follow up was lower in scalpel blade surgery as compared to cryosurgery category, Diode LASER category, and CO_2 LASER category. The findings were significant statistically (p=0.001). There was decrease in slough in all treatment modalities at two week follow up. The proportion of slough at two week follow up in scalpel blade category was minimum as compared to cryosurgery category, Diode LASER category, and CO_2 LASER category (p=0.004). The incidence of slough in cryosurgery category, Diode LASER category and CO_2 LASER category was comparable at first week and second week follow up **(Table 8).** The proportion of patients with recurrence at 3 months follow up and 6 months follow up was lower in scalpel blade surgery as compared to cryosurgery category, Diode LASER category, and CO_2 LASER category. The findings were significant statistically (p=0.001). There was decrease in recurrence in all treatment modalities at 6 month follow up. The proportion of recurrence at 6 months follow up in scalpel blade category was minimum as compared to cryosurgery category, diode LASER category, and CO_2 LASER category (p=0.002). The incidence of recurrences in cryosurgery category, diode LASER category and CO_2 LASER category was comparable at 3 months and 6 months follow up **(Table 9).**

Discussion:

Data shows that pain at ay of surgery and bleeding was greater in conventional scalpel and blade surgery as compared to diode LASER, CO_2 LASER and cryo-theraphy **[16-21].** It was also observed in some studies that pain in cryotherapy was greater than LASERS. This finding is not similar to our study where pain in cryotherapy was lesser as compared to LASER **[26].** The first step in treating OPMDs is to remove risk factors such smoking, using tobacco products, quitting betel quid, and reducing or quitting alcohol entirely **[11–14].** The prognosis may change significantly if smoking is completely stopped. The course of treatment will also depend on the severity of the lesion, including its location, size, and position, as well as any concomitant dysplasia **[15–17].** To manage OPMDs, a variety of medication and surgical therapeutic approaches are employed. The goal of treating OPMD is to reverse or totally eradicate the changes to the oral mucosa **[13–16].** Topical and systemic medications, with differing degrees of success, include vitamin A and retinoid, lycopene, ketorolac, systemic beta-carotene, topical and systemic corticosteroids, and local bleomycin in the medical line of care for OPMD.

There was low proportion of patients with oedema in cryosurgery group as compared to Diode LASER, scalpel blade surgery and CO_2 LASER at one week follow up. The findings were significant statistically (0.001). There was decrease in oedema in all treatment modalities at two week follow up. The proportion of oedema in at two week follow up in different treatment modalities was comparable (p=0.89**).** The proportion of patients with infection was comparable in cryosurgery category, Diode LASER category , scalpel blade surgery and CO_2 LASER category at one week follow up (p=0.71). There was decrease in infection in all treatment modalities at two week follow up. The proportion of infection in at two week follow up in different treatment modalities was comparable (p=0.34). Data have showed comparable oedema in different surgical treatment modalities for OPMDs **[2-6].** Some study has shown than oedema is greater in cryotherapy as compared to LASER. This finding is not similar to our study where oedema is lesser in cryotherapy **[27].**

Although vitamin A, or retinoid, has been used medicinally, there is little evidence from research to substantiate its effectiveness in reducing the incidence of cancer transformation and relapse **[4–11].** Among the surgical procedures that have been suggested for the management of OPMDs are LASER surgery and traditional surgery with a scalpel and blade **[5–12].** Conventional surgeries are limited by the disease's location and extent. Cryosurgery is a simple, safe, and effective treatment for several benign and precancerous lesions of the oral cavity, as well as OPMDs **[13–15].** Lasers have many benefits over traditional surgery, such as targeted excision, simple homeostasis maintenance, and reduced postoperative pain and oedema **[16–18].** While cryotherapy has proven effective in managing several medical surgeries, its application in the treatment of OPMDS remains an area of on-going investigation **[20, 21].** These findings are having similarity with findings of previous study where scar and recurrence at 3 months follow up and 6 months follow up was lower in scalpel blade surgery as compared to cryosurgery category, diode LASER category, and CO_2 LASER category [10-16]. Some previous studies like our study showed that the incidence of scar in cryosurgery category, diode LASER category and CO_2 LASER category was comparable at 3 months and 6 months follow up **[12-18].** There were some studies in past which have shown similar results for scalpel blade surgery and cryotherapy regarding development of slough **[12-16].** Randomized clinical trials have not been used to evaluate the efficacy of surgical management in preventing recurrent OPMDs and afterwards transformation into cancer, data showed that all four surgical modalities were effective in treating OPMDs.

Conclusion:

Data shows that all four surgical modalities were effective for treatment of OPMDs. It further showed that cryotherapy seems to offer better clinically significant results than laser therapy.

References:

[1] Babu KG. *Semin in Oncol.* 2001 **28**:169. [PMID: 11301379]
[2] Goharkhay K *et al Lasers Surg Med.* 1999 **25**:401. [PMID: 10602132]
[3] Zeinoun T *et al. Lasers Surg Med.* 2001 **28**:74. [PMID: 11430446]
[4] Lodi G *et al. Cochrane Database Syst Rev.* 2016 **7**:Cd001829. [PMID: 27471845]
[5] Frame JW *et al. J Oral Maxillofac Surg.* 1985 **43**:850. [PMID: 3932616]
[6] Kardos TB *et al. Int J Oral Maxillofac Surg.* 1989 **18**:117. [PMID: 2501405]
[7] Warnakulasuriya S *et al. J Oral Pathol Med.* 2016 **45**:155. [PMID: 26189354]
[8] Huang Z *et al. J Craniofac Surg.* 2015 26:e277. [PMID: 25974830]
[9] Flynn MB *et al. J Surg Oncol.* 1988 **37**:232. [PMID: 3361914]
[10] Van der Waal I *et al. Oral Oncol.* 1997 **33**:291. [PMID: 9415326]
[11] Ben-Bassat M *et al. Br J Plast Surg.* 1978 **31**:155. [PMID: 565230]
[12] Akbulut N *et al. Eur J Dent.* 2013 **7**:207. [PMID: 24883028]
[13] Napier SS *et al. J Oral Pathol Med.* 2008 **37**:1. [PMID: 18154571]
[14] Sako K *et al. Am J Surg.* 1972 **124**:482. [PMID: 5076162]
[15] Yeh CJ. *Int J Oral Maxillofac Surg.* 2000 **29**:212 [PMID: 10970086]
[16] Shiu MN *et al. Br J Cancer.* 2000 **82**:1871. [PMID: 10839305]
[17] Lodi G *et al J Dent Educ.* 2002 **66**:896. [PMID: 12214837]
[18] Kawczyk-Krupka A *et al. Photodiagnosis Photodyn Ther.* 2012 9:148. [PMID: 22594985]
[19] Ishii J *et al. Oral Oncol.* 2003 **39**:759. [PMID: 13679199]
[20] Yu CH *et al. J Formos Med Assoc.* 2014 113:272. [PMID: 24560447]

[21] Gupta PC *et al*. *Oral Dis*. 1995 **1**:54. [PMID: 7553382]

[22] Ribeiro AS *et al*. *Int J Dent*. 2010 **2010**:186018. [PMID: 20339486]

[23] Lin HP *et al*. *Head Neck*. 2012 **34**:1306. [PMID: 22084001]

[24] Kumar A*et al*. *Br J Oral Maxillofac Surg*. 2013 **51**:377. [PMID: 23159193]

[25] Hong WK *et al*. *N Engl J Med*. 1986 **315**:1501. [PMID: 3537787]

[26] Natekar M *et al*. *J Clin Exp Dent*. 2017 **9**:e779. [PMID: 28638555]