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The efficacy and safety of intramuscular aceclofenac and diclofenac for managing postoperative pain in patients undergoing composite resection for oral cancer

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Abstract

Aim: Non-steroidal anti-inflammatory drugs are the most used analgesics for postoperative pain management. Aceclofenac is a newer phenylacetic acid derivative, and being a predominant cyclooxygenase-2 inhibitor, it has better gastrointestinal tolerability than diclofenac. The aim was to compare the efficacy and safety of aceclofenac and diclofenac in managing postoperative pain using the Face Legs Activity Cry Consolability (FLACC) score and a visual analog scale (VAS) following composite resection for oral cancer.

Methods: Seventy-six patients who underwent composite resection for oral cancer at a tertiary care hospital were randomly assigned to receive either injection of aceclofenac 150 mg or diclofenac 75 mg intramuscularly at 0, 12, 24, 36, 48, and 60 h postoperatively. The FLACC score was recorded at 2, 4, 8, 12, and 24 h, and the VAS score was recorded at 24, 36, 48, 60, and 72 h. Intravenous tramadol 100 mg was given as a rescue analgesic if the FLACC or VAS score was > 3. The patient satisfaction score was recorded at 72 h.

Results: There were 61 female and 15 male patients. Mean surgery durations in the aceclofenac and diclofenac groups were 450.00 ± 116.00 and 416.84 ± 130.63 minutes, respectively. Mean FLACC scores between the two groups were not significantly different. Patients receiving diclofenac had significantly lower mean VAS scores (P = 0.005) at 72 than at 24 h. There was no significant difference in mean VAS scores between groups. The amount of rescue analgesic required in both groups was similar (P = 0.34). At 72 h, 31.57% of patients graded their satisfaction as good in the aceclofenac group and 34.21% in the diclofenac group. Nausea and dyspepsia were common adverse effects in both groups.

Conclusion: Aceclofenac was as effective as diclofenac in reducing postoperative pain following composite resection for oral cancer. In individuals with a history of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac.

Keywords: Oral cancer, aceclofenac, diclofenac

INTRODUCTION

Head and neck cancer accounts for 30%-32% of all cancers in India, and oral cancer is the most common. In patients undergoing surgery, measuring pain is critical[1,2]. Non-steroidal anti-inflammatory drugs (NSAIDs) are usually combined with opioids to reduce doses of the latter and their associated adverse effects[3].

Diclofenac sodium is a potent, commonly prescribed drug for pain relief. It is a nonselective cyclooxygenase inhibitor that inhibits the production of prostaglandin, a critical pain mediator. The drug reduces postoperative pain by decreasing nociceptive transmission to the brain[4]. Diclofenac is rapidly absorbed as a sugar-coated tablet, rectal suppository, or intramuscular injection. Only 50% of the drug reaches the systemic circulation unchanged following first-pass metabolism, and 99% is bound to plasma proteins. Diclofenac is predominantly eliminated through hepatic biotransformation, with less than 1% of the dose excreted unchanged through the kidneys. Its hydroxylated metabolites undergo glucuronidation and sulfation and are excreted in the urine[4,5]. Diclofenac is associated with adverse effects such as nausea, epigastric pain, peptic ulcer, maculopapular rash, and fixed drug eruptions[6].

Aceclofenac is a newer phenylacetic acid derivative with anti-inflammatory properties similar to diclofenac. It is a predominant cyclooxygenase-2 inhibitor and has better gastrointestinal tolerability. It interferes with neutrophil adhesion to endothelium and inhibits PGE2. It also decreases the expression of interleukin-1 and tumor necrosis factor-alpha, resulting in analgesia and anti-inflammation[7]. Aceclofenac is absorbed from the gastrointestinal tract, and the peak plasma concentration is reached at 1 to 3 h after an oral dose[7]. The drug is also administered intramuscularly at 150 mg twice or thrice daily for postoperative pain management[5]. Aceclofenac is more than 99% plasma protein-bound and has a plasma elimination half-life of about 4 h. About two-thirds of a dose is excreted in the urine, primarily as hydroxy metabolites[8-10].

Aceclofenac is associated with a lower incidence of myocardial infarction and atherosclerosis than other selective cyclooxygenase-2 inhibitors[11]. This present study was undertaken to compare the efficacy and safety of these drugs for postoperative pain management in patients undergoing composite resection for oral cancer.

MATERIALS AND METHODS

This was a prospective and open-label study conducted by the Departments of Pharmacology and Otorhinolaryngology on patients admitted to the Departments of Otorhinolaryngology and Head and Neck Surgery in a tertiary care hospital affiliated with a medical college. The study was carried out over one and a

half years. The institutional ethics committee approved the protocol (No. DMC/KLR/IEC/CER/58/2015-16 dated 09-11-2015), and written informed consent was obtained from all participants.

We recruited 76 patients randomly divided into two groups by a lottery method. Patients of either gender aged between 25 to 70 years undergoing composite resection for oral cancer were included. We excluded patients on radiotherapy, those who had prior surgery for oral cancer, those who had received NSAIDs or opioids 12 h before surgery, those who had a history of peptic ulcer, gastrointestinal bleeding, asthma, chronic obstructive lung disease, or hypersensitivity to the study medications, and those who were pregnant or lactating.

Patients undergoing composite resection for oral cancer were randomly assigned by a lottery method to groups A or D, with 38 patients in each group. Both groups received a fentanyl 25 mcg transdermal patch immediately after surgery. Patients in group A received aceclofenac 150 mg, and group D received diclofenac sodium 75 mg intramuscularly immediately after recovery from anesthesia. 12 h after this dose, the study medication was repeated. On the first and second postoperative days, patients received the same dose of the drugs twice daily in the respective groups. Six doses of the study drugs were given 12 h apart.

The Face, Legs, Activity, Cry, Consolability (FLACC) is used in adults who cannot communicate. It is based on observations regarding the patient's face, the position of their legs, their actions, and whether they are calm or consolable. Zero to two points were assigned for each of these five observation areas. The score was graded as follows: (0 = Relaxed and comfortable, 1-3 = Mild discomfort, 4-6 = Moderate pain, 7-10 = Severe discomfort/pain)[12]. The FLACC score was recorded at 2, 4, 8, 12, and 24 h postoperatively. The visual analog scale (VAS) score was graded from 0 to 10 (0 = no pain and 10 = worst pain)[13]. The scores were explained and recorded at 24, 36, 48, 60, and 72 h postoperatively.

Pulse rate, blood pressure, and respiratory rate were monitored immediately after recovery from anesthesia and at 2, 4, 8, 12, and 24 h postoperatively. The rescue analgesic (tramadol 100 mg intravenously) was given to the patients if the FLACC or VAS scores were more than three during the postoperative period. Patient satisfaction scores were recorded at 48 and 72 h. Adverse effects were recorded and analyzed following the World Health Organization causality assessment scale.

Statistical methods

To detect a mean difference of 1.16 in the VAS score at the end of 8 h postoperatively with an effect size of 0.63, alpha error of 5%, and power of 80% with a dropout rate of 10%, the required sample size was calculated to be 38 in each group. The demographic data were analyzed using descriptive statistics. The FLACC and VAS scores were assessed within the group using repeated-measures analysis of variance and between the groups using an unpaired t-test. Adverse effects were analyzed using the chi-square test. *P*-values less than 0.05 were considered significant.

RESULTS

We randomly allocated 76 patients undergoing composite resection for oral cancer under general anesthesia to groups A and D. All patients received a fentanyl 25 mcg transdermal patch following recovery from anesthesia. Figure 1 represents patient recruitment, medication, and follow-up. Seventy-five patients completed the study.

The demographic parameters were comparable in both groups. TNM staging is explained in Table 1. All patients had locally advanced disease (T3 or T4a). The lesions involved the buccal mucosa and the lower

Table 1. Demographics

Variables	Group A N = 38	Group D N = 38
Male/female	7/31	8/30
Age (years) (Mean ± SD)	56.44 ± 10.89	52.87 ± 11.89
Duration of surgery (minutes) (Mean ± SD)	450.00 ± 116.00	416.84 ± 130.63
T_3/T_{4a} stage of oral cancer	7/31	15/23
T4aN1Mx	19	15
T4aN2bMx	03	03
T4aN2Mx	03	00
T4aN2cMx	02	02
T4aN0Mx	01	01
T4N0M0	01	00
T4bN2Mx	01	00
T4aN2Mx	01	00
T4N2aMx	00	01
T4N0Mx	00	01
T3N1Mx	03	05
T3N0Mx	02	07
T3N2aMx	01	00
T3N2aM0	00	01
T3N2bMx	00	02
T3aN0Mx	01	00

gingivobuccal sulcus; therefore, it was not possible to determine the subsite of origin. The squamous cell carcinoma of the buccal mucosa contributed to 97%, and the remainder were verrucous. Among 76 patients, 15 were males, and 61 were females, with a literacy rate of 7.6%. An increase in mean FLACC scores was observed in both groups at 4, 8, 12, and 24 h postoperatively following recovery from anesthesia. The difference between the groups was not statistically significant at any time [Table 2]. The mean VAS score increased in patients at 36 h in both groups and decreased by 72 h. The reduction in VAS score at 72 h was statistically significant compared to 24 h in patients who received diclofenac ($P = 0.005$) [Table 3].

The reduction in mean VAS scores between medications was not significant at any time [Table 3]. The reduction of postoperative pain at all time intervals was similar in patients receiving either medication. The area under the curve for reducing postoperative pain in patients receiving medications [Figure 2] was calculated using the trapezoid method. The pain intensity from 24 to 72 h was lower with diclofenac (0.88) than with aceclofenac (0.94). The association of FLACC at 2 hrs and 24 hrs and VAS at 24 h and 72 h with age, gender, and cancer stage was assessed using Pearson's correlation with both medications [Table 4]. There was no correlation between the pain scores and the parameters for which it was evaluated.

Intravenous tramadol 100 mg was given as the rescue analgesic. Patients in group A received the first rescue analgesic earlier than those in group D, but the difference was insignificant. The amount of tramadol used in both groups was comparable [Table 5]. Kaplan-Meier curves [Figure 3] represent the time from administering the study drug to the first rescue analgesic used. The log-rank test (0.429) indicates no significant difference in the probability of patients receiving the first rescue analgesic with either medication at any time. Blood pressure and heart rates were within normal range and did not significantly differ between groups.

Table 2. Comparison of mean FLACC scores between two groups

	FLACC score (Mean ± SD)				
	2 h	**4 h**	**8 h**	**12 h**	**24 h**
Group A N = 37	0.94 ± 0.37	1.10 ± 0.65	1.66 ± 0.58	1.71 ± 0.56	1.84 ± 0.54
Group D N = 38	1.02 ± 0.49	1.28 ± 0.51	1.42 ± 0.68	1.58 ± 00	1.86 ± 0.66
**P*-value	0.42	0.18	0.10	0.15	0.88

*Unpaired t-test.

Table 3. Post-operative pain score (VAS) within the group and between two groups

	Group A N = 37		Group D N = 38		
Time postoperatively	**Mean ± SD**	**#P value**	**Mean ± SD**	**#P-value**	**##P-value**
24 h	2.61 ± 0.75		2.47 ± 0.56		0.39
36 h	3.37 ± 1.36	0.001*	3.29 ± 1.50	0.002*	0.91
48 h	2.84 ± 1.10	0.15	2.55 ± 1.30	0.73	0.18
60 h	2.47 ± 0.92	0.40	2.39 ± 0.91	0.69	0.70
72 h	2.47 ± 1.13	0.47	2.08 ± 0.54	0.005*	0.05

#R-ANOVA; ##Unpaired t-test.

Table 4. Comparison of FLACC and VAS with different parameters between the groups

		Aceclofenac			Diclofenac		
FLACC		**Age**	**Gender**	**Cancer stage**	**Age**	**Gender**	**Cancer stage**
2 h	r	0.08	-0.06	0.06	0.25	-0.23	-0.17
	p	0.63	0.70	0.70	0.13	0.15	0.28
24 h	r	0.18	0.11	-0.13	0.27	-0.005	-0.16
VAS	p	0.25	0.50	0.40	0.09	0.97	0.33
24 h	r	0.17	0.02	0.02	0.21	-0.20	-0.08
	p	0.30	0.39	0.89	0.18	0.88	0.60
72 h	r	0.10	0.08	0.14	0.25	0.07	-0.08
	p	0.52	0.36	0.40	0.62	0.64	0.62

r: Pearson correlation coefficient; p: *P* value.

Table 5. Patients requiring rescue analgesia

	Group A N = 37 (Mean ± SD)	**Group D N = 38 (Mean ± SD)**	***P*-value**
No. of patients receiving Tramadol	13	12	
Time to first rescue analgesic (h)	43.38 ± 10.44	44.00 ± 09.34	0.88
Total amount of Tramadol (mg) used	115.38 ± 37.55	108.33 ± 28.88	0.34

At the end of 48 h, 64.9% of patients graded their satisfaction score as fair and 29.8% as good in group A, whereas 60.6% graded satisfaction as fair and 31.6% as good in group D. At the end of 72 h, 56.6% of patients graded their satisfaction score as fair and 32.4% as good in group A, whereas 55.3% graded it as fair and 34.2% as good in group D [Table 6].

Table 6. Number of patients expressing satisfaction at various time points

	Aceclofenac		Diclofenac	
Score	48 h	72 h	48 h	72 h
Poor	02	04	03	04
Fair	24	21	23	21
Good	11	12	12	13

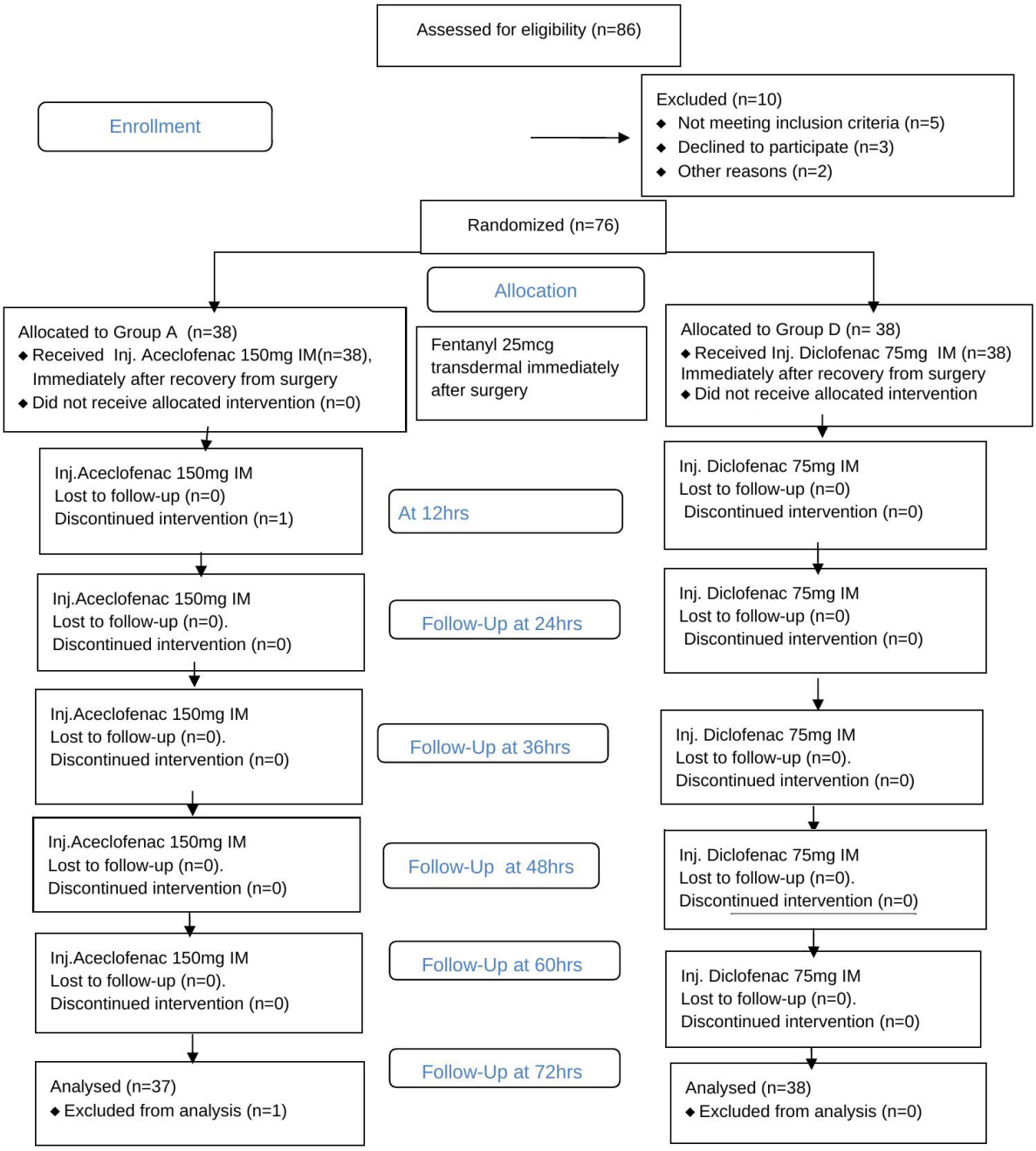

Figure 1. Consort flow chart representing recruitment, randomization and follow up.

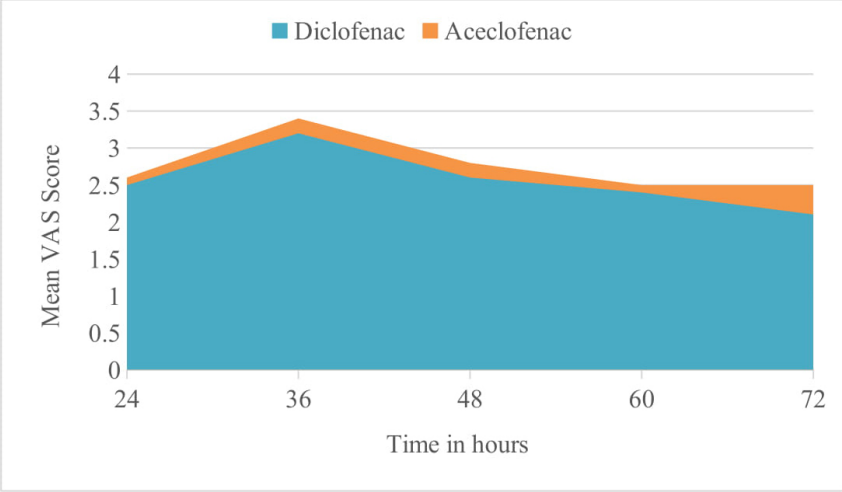

Figure 2. Area under the curve for Aceclofenac and diclofenac.

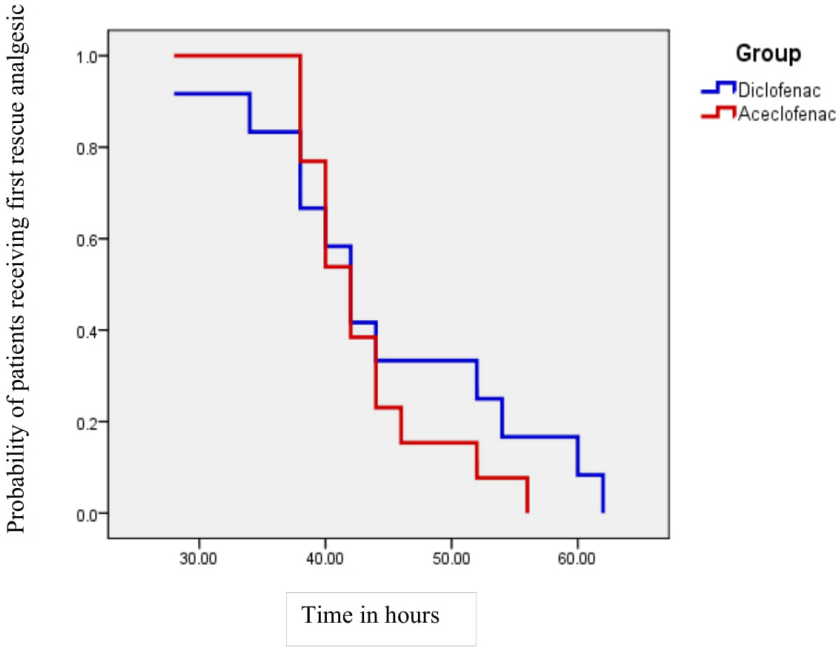

Figure 3. Kaplan Meier curve for first rescue analgestic between two groups.

One patient in group A was excluded when they developed rash and hypotension following the first dose of injection aceclofenac. The total number of adverse effects noted was ten in group A and 14 in group D [Figure 4]. The most common adverse effects were nausea and epigastric discomfort, which did not significantly differ in patients receiving either medication. Patients with the most side effects were older in the aceclofenac group than the diclofenac group (61 *vs.* 45 years). Diclofenac is predominantly eliminated through hepatic biotransformation, with less than 1% of the dose excreted unchanged through the kidneys[4,5]. For aceclofenac, about two-thirds of a dose is excreted in the urine, mainly as hydroxy metabolites[8]; therefore, there was probably no effect on the kidneys in both groups.

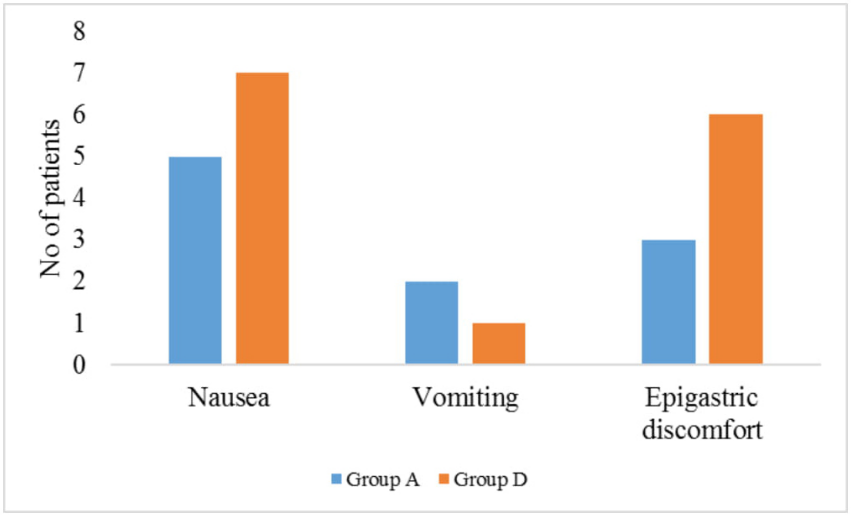

Figure 4. Adverse effects in both groups.

DISCUSSION

In India, the incidence of oral cancer is 20 cases per 100,000 population and accounts for over 30% of all cancers[14]. Head and neck cancer is the most common cancer in males; it is second to cervical cancer in females. Oral cancers occur due to the use of smokeless forms of tobacco, such as betel nut, gutkha, and paan, which are common in India. These substances are placed in the oral cavity for prolonged periods. Most patients approach the surgeon when the lesions are in stage 3 or 4. Oral cancers are usually resected surgically with or without adjuvant radiotherapy or chemotherapy based on the invasion of the surrounding structures[15,16]. The patients in our study were in stages T3 and T4a. Resection of cancerous lesions of the oral cavity is associated with severe pain, the intensity of which depends on the site of surgery and the extent of tissue damage[17-19].

Opioids and NSAIDs are the mainstays for treating moderate to severe postoperative pain[20]. Because NSAIDs are devoid of opioid-related adverse effects, we compared aceclofenac and diclofenac in postoperative pain management following composite resection for oral cancer. Of the 76 patients, 80% were females and 20% males; this discrepancy can be attributed to females tending to stack tobacco in the lower gingiva for extended periods and males smoking *beedi*. Similar findings were reported in a study conducted in a Spanish Caucasian population, where 57.4% of patients with oral cancer were females[16]. In our study, the patients were 40-70 years old, which agrees with another study conducted in a tertiary care hospital in Rajasthan, where the average age of presentation of oral cancer was 50.4 years[15].

Most patients (71%) presented when the tumor was in stage T4a. Often, there is a considerable delay in diagnosing oral cancers in India; despite the relative ease of oral cavity examination, self-examination by patients themselves has not been routinely practiced. The other reasons for late diagnosis are ignorance of patients, lack of awareness, and inadvertent delay in treatment in rural areas[15]. Histopathological examination revealed that 97% of patients had squamous cell carcinoma and 3% verrucous carcinoma, also a squamous cell carcinoma variant; a similar finding was reported in another study[15].

There were 76 patients recruited [Figure 1]; none were in the T1/T2 stage. All patients required composite resection for locally advanced disease (T3/T4a). The only difference between T3 and T4a is the involvement of skin or bone in T4a; however, all patients underwent composite resection (including segmental

mandibulectomy and modified radical neck dissection) for either bone invasion or to achieve adequate surgical margins. Reconstruction of the defect was similar in all patients (pectoralis major myocutaneous flap); therefore, we expected the severity of pain to be similar in both groups. The duration of surgery was comparable in both groups.

The FLACC score was used to assess the pain intensity during the first 24 h since the patients could not communicate orally due to endotracheal intubation or partial resection of the mandible/structures around it. The FLACC score increased over 24 h in both treatment groups but remained below three, representing mild pain [Table 2]. This finding was probably because the patients were under the weaning phase of the anesthetic, the influence of the postoperative transdermal fentanyl patch, and the administration of study drugs.

There was a reduction of pain as indicated by the VAS score [Table 3] at the end of 72 h compared to 24 h; however, this reduction was significant in patients receiving diclofenac. Other studies revealed a significant reduction in VAS scores in patients receiving flupirtine or diclofenac following craniotomy[21]. When morphine and diclofenac suppositories were used following coronary artery bypass surgeries, both medications were equally efficacious in reducing postoperative pain from extubation until 72 h[22].

We observed that the reduction in pain by aceclofenac and diclofenac was always similar [Table 3]. By contrast, a study reported that intramuscular aceclofenac was superior to diclofenac in lower limb surgery; in another study, oral aceclofenac was better than diclofenac for relieving pain following extraction of the third molar[23,24].

In our study, the intensity of pain experienced by the patients was denoted by the area under the curve. Patients receiving diclofenac (0.88) had marginally better pain control than those receiving aceclofenac (0.94) [Figure 2]. The time to first rescue analgesic was not significantly different between the groups, as represented by the Kaplan-Meier curve [Figure 3]. A study from Turkey showed that consumption of tramadol was lowest in patients receiving diclofenac than lornoxicam or dexketoprofen after 24 h[25]. Another study has shown that intramuscular diclofenac was equally effective as a combination of diclofenac and paracetamol regarding rescue analgesic requirement, suggesting that the combination conferred no advantage[26].

We recorded the patient satisfaction score at the end of 48 and 72 h. The pain relief was better with diclofenac at 48 h but similar to aceclofenac at 72 h. This finding contrasted with a study by Sharma *et al*., where 60% of patients who received aceclofenac expressed their pain relief as excellent following lower limb surgeries compared to diclofenac[23].

The adverse effects, such as nausea and epigastric discomfort [Figure 4], were higher with diclofenac, similar to a study comparing diclofenac with aceclofenac following third molar surgery[24]. One patient in our study developed a maculopapular rash and hypotension following the first dose of aceclofenac, and the drug was discontinued.

The findings of our study suggest that early pain relief in the postoperative period was better with diclofenac; however, in the later part, the efficacy of both drugs was similar. In individuals with a history or risk of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac.

In conclusion, Aceclofenac was as effective as diclofenac in reducing postoperative pain following composite resection for oral cancer. In individuals with a history of gastritis or peptic ulcer, aceclofenac can be an alternative to diclofenac.

DECLARATIONS

Authors' contributions

Design, literature search, data acquisition and analysis, manuscript preparation: Ganashree P
Concept, design, data and statistical analysis, manuscript review, and editing: Sarala N
Material support, data interpretation, manuscript editing: Azeem Mohiyuddin SM

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The institutional ethics committee approved the study, and informed consent was obtained from the participants.

Consent for publication

The participants agreed to participate in this study and gave consent for publication.

REFERENCES

1. Sidransky D. Cancer of head and neck. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer principles and practice of oncology, 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2005. pp. 653-8.
2. Gil Z, Smith DB, Marouani N, Khafif A, Fliss DM. Treatment of pain after head and neck surgeries: control of acute pain after head and neck oncological surgeries. *Otolaryngol Head Neck Surg* 2006;135:182-8. DOI PubMed
3. Smirnov G, Terävä M, Tuomilehto H, Hujala K, Seppänen M, Kokki H. Etoricoxib for pain management during thyroid surgery-a prospective, placebo-controlled study. *Otolaryngol Head Neck Surg* 2008;138:92-7. DOI PubMed
4. León-Reyes MR, Castañeda-Hernández G, Ortiz MI. Pharmacokinetics and pharmacodynamics of diclofenac in the presence and absence of glibenclamide in the rat. *J Pharm Pharm Sci* 2008;11:68-76. DOI PubMed
5. Grosser T, Smyth EM, Fitzgerald GA. Anti-inflammatory, antipyretic and analgesic agents; pharmacotherapy of gout. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: Mc Graw Hill; 2011. pp. 959-1005.
6. Chunduri NS, Kollu T, Goteki VR, Mallela KK, Madasu K. Efficacy of aceclofenac and diclofenac sodium for relief of postoperative pain after third molar surgery: a randomised open label comparative study. *J Pharmacol Pharmacother* 2013;4:144-5. DOI PubMed PMC
7. Patil AK, Gangurdi AB, Amin PD. Comparative study of different formulations of aceclofenac topical drug delivery system and its in vtiro and in vivo characterization. *Int J Pharm Sci Res* 2014;5:3401-08. DOI
8. Sweetman SC. Martindale the complete drug reference, 38th ed. UK: Pharmaceutical Press; 2014. pp. 3-142.
9. Gavhana YN, Yadav AV. Improvement in histochemical properties of aceclofenac by using chitosan and water soluble chitosan. *Ind J Pharm Pharm Sci* 2013;5:414-19. Available from: https://web.archive.org/web/20180413062808id_/http://ijppsjournal.com/Vol5Suppl1/6483.pdf [Last accessed on 21 March 2023]
10. Maheshwari RK, Indurkya A. Formulation and evaluation of aceclofenac injection made by mixed hydrotropic solubilization technique. *Iran J Pharm Res* 2010;9:233-42. PubMed PMC

11. Solanki SS, Dahima R. Formulation and evaluation of aceclofenac mouth-dissolving tablet. *J Adv Pharm Technol Res* 2011;2:128-31. DOI PubMed PMC
12. Voepel-Lewis T, Zanotti J, Dammeyer JA, Merkel S. Reliability and validity of the face, legs, activity, cry, consolability behavioral tool in assessing acute pain in critically ill patients. *Am J Crit Care* 2010;19:55-61. DOI PubMed
13. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14:798-804. DOI PubMed
14. Sankaranarayanan R, Ramadas K, Thomas G, et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 2005;365:1927-33. DOI PubMed
15. Sharma RG, Bang B, Verma H, Mehta JM. Profile of oral squamous cell cancer in a tertiary level medical college hospital: a 10 yr study. *Indian J Surg Oncol* 2012;3:250-4. DOI PubMed PMC
16. Candau-Alvarez A, Dean-Ferrer A, Alamillos-Granados FJ, et al. Verrucous carcinoma of the oral mucosa: an epidemiological and follow-up study of patients treated with surgery in 5 last years. *Med Oral Patol Oral Cir Bucal* 2014;19:e506-11. DOI PubMed PMC
17. Lewandowska A, Filip R, Mucha M. Postoperative pain combating and evaluation of patient's satisfaction from analgesic treatment. *Ann Agric Environ Med* 2013;1:48-51. PubMed
18. Mahran E, Hassan ME. Comparison of pregabalin versus ketamine in postoperative pain management in breast cancer surgery. *Saudi J Anaesth* 2015;9:253-7. DOI PubMed PMC
19. Peng Z, Li H, Zhang C, Qian X, Feng Z, Zhu S. A retrospective study of chronic post-surgical pain following thoracic surgery: prevalence, risk factors, incidence of neuropathic component, and impact on qualify of life. *PLoS One* 2014;9:e90014. DOI PubMed PMC
20. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ* 2014;348:g1251. DOI PubMed PMC
21. Yadav G, Choupoo S, Das SK, et al. Evaluating the role of flupirtine for postcraniotomy pain and compare it with diclofenac sodium: a prospective, randomized, double blind, placebo-controlled study. *J Neurosurg Anesthesiol* 2014;26:32-6. DOI PubMed
22. Imantalab V, Mirmansouri A, Sedighinejad A, et al. Comparing the effects of morphine sulfate and diclofenac suppositories on postoperative pain in coronary artery bypass graft patients. *Anesth Pain Med* 2014;4:e19423. DOI PubMed PMC
23. Sharma V, Awasti B, Rana S, Sharma S. Comparison of efficacy of diclofenac versus aceclofenac in post operative pain in lower limb fractures: a double blind, randomized study. *Int J Ortho Surg* 2012;19:1-15. Available from: https://www.semanticscholar.org/paper/Comparison-of-Efficacy-of-Diclofenac-versus-in-Post-Sharma-Awasthi/40d945e77f328b096612f237aa5cc7c59802e842 [Last accessed on 21 March 2023]
24. Kılıçkaya R, Güleç E, Ünlügenç H, Gündüz M, Işık G. A comparative study of the efficacy of IV dexketoprofen, lornoxicam, and diclophenac sodium on postoperative analgesia and tramadol consumption in patients receiving patient-controlled tramadol. *Turk J Anaesthesiol Reanim* 2015;43:174-80. DOI PubMed PMC
25. Pal A, Biswas J, Mukhopadhyay P, Sanyal P, Dasgupta S, Das S. Diclofenac is more effective for post-operative analgesia in patients undergoing lower abdominal gynecological surgeries: a comparative study. *Anesth Essays Res* 2014;8:192-6. DOI PubMed PMC
26. Joshi A, Patil VM, Noronha V, et al. Diclofenac versus tramadol for mucositis related pain in head and neck cancer patients undergoing concurrent chemoradiation-a phase 3 study. *Ecancermedicalscience* 2021;15:1318. DOI PubMed PMC