Opioid sparing effect of diclofenac sodium when used as an intra-operative analgesic during maxillofacial cancer surgeries

INTRODUCTION

Oral cavity cancers are one of the most common cancers in Indian males. Consequently, maxillofacial cancer surgery constitutes a large part of surgical oncology practice in India. Manipulation and excision of mandible, maxilla and tongue are extremely noxious stimuli and severe hypertension and tachycardia during these procedures is not unusual. Management includes deepening the plane of anaesthesia by increasing the inhalational anaesthetic concentration and addition of intravenous (IV) opioids.

Traditionally, strong analgesics such as opioids have been used intra-operatively whereas non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol are most commonly given at the end of surgery as part of multimodal approach to post-operative analgesia.[1,2] NSAIDs are highly effective in controlling bone pain and have analgesic effects in various conditions especially where tissue inflammation contributes to pain.[3,4] Concerns regarding the deleterious effects of NSAIDs on platelet function and renal function in conditions of renal hypoperfusion are some of the reasons why NSAIDs are not preferred as intra-operative

analgesics. In cancer patients, many commonly used chemotherapeutic drugs have known nephrotoxic effects. Drugs such as cisplatinum and ifosfamide cause tubular damage whereas bevacizumab and gemcitabine injure renal vasculature. Hence, there is a tendency to restrict use of NSAIDs in these patients.

We hypothesized that addition of single dose of diclofenac at the time of induction would exert opioid sparing effect during intra-operative period and reduce surges in blood pressure (BP) and pulse rate during noxious stimuli.

METHODS

This prospective, double-blind, randomised, placebo-controlled study was conducted in a tertiary care cancer hospital. Institutional Review Board approval was obtained prior to the study. Eligible subjects were enrolled in the study after written informed consent.

The subjects included 100 adult patients more than 18 years of age posted for maxillofacial surgery with reconstructive surgery. Patients known to have allergy to the study drugs, bleeding disorders, pregnancy, acid-peptic disorder, heart ailments such as congestive cardiac failure, liver and kidney diseases were excluded from the study. Patients were also excluded if they were already on treatment with NSAIDs, opioids, anticoagulants, methotrexate, cyclosporin, lithium or phenytoin.

The patients recruited to the study were randomised prior to anaesthesia to either Group 1 (Placebo Group) to receive 100 cc normal saline after induction of anaesthesia and Group 2 (Diclofenac Group) to receive diclofenac sodium 1 mg/kg in 100 cc normal saline IV after induction of anaesthesia.

We selected sample size of 100 based on convenience. Patients were randomised based on the date of surgery. Patients operated on odd days were recruited to Group 1 whereas those operated on even days were recruited to Group 2. Patients, attending doctors including the anaesthesiologist and the recovery room staff were blinded to the study group.

Primary outcome was difference in opioid consumption between two groups and secondary end points were pain score and sedation score in recovery. Pain scores using visual analogue scale [VAS] and sedation score, using University of Michigan Sedation Scale [Table 1][5,6] were measured by recovery nurse as part of vital signs monitoring on arrival and every hour and reported to investigator/recovery area physician. Study investigators independently recorded pain and sedation score 4th hourly. In post-operative period, rescue analgesic buprenorphine 3 μ/kg IM was given at VAS ≥4. If patient had pain, he/she would also use sign language to communicate with attending physician or nurse.

Anaesthesia was induced with fentanyl 2 μ/kg followed by thiopentone 3–5 mg/kg. Muscle relaxation was achieved with succinylcholine 2 mg/kg or vecuronium bromide 0.1 mg/kg as indicated. Anaesthesia was maintained with O_2 + N_2O (40:60) and isoflurane 1.5% dialed concentration for first 15 min which was reduced to 0.8% thereafter and total gas flows of 1 to 1.5 L/min. Both groups received continuous infusion of IV fentanyl 1 μ/kg/h as the standard analgesic. During surgery, BP and pulse rate above 20% of baseline values were considered as signs of inadequate analgesia and were treated with an additional bolus dose of IV fentanyl 1 μ/kg, which could be repeated at 5 min interval as required since peak action of fentanyl occurs at 3–5 min.[7] Fall in BP was treated with fluid boluses. Bradycardia was treated by stopping surgical manipulations and if bradycardia persisted, injection atropine 0.6 mg IV was administered. At the end of surgery, fentanyl infusion was stopped. The neuromuscular block was reversed with IV neostigmine 0.05 mg/kg and IV glycopyrrolate 8 μg/kg. The endotracheal tube was left *in situ* overnight for airway maintenance.

All patients received standard post-operative care. The time of first demand for analgesic after admission to PACU was noted.

RESULTS

The demographic variables were comparable in both the groups [Table 2]. Majority of patients were male (86% and 78% in Group 1 and Group 2, respectively). The average age in both groups was 47 years (30–65 years) and 74%

Table 1: Sedation scale

Level of sedation	Feature
0	Awake and alert
1	Mildly sedated
2	Moderately sedated
3	Deeply sedated
4	Unarousable

of the patients belonged to the American Society of Anaesthesiologists I physical status. The mean duration of surgery was around 320 min (210–370 min).

Patients in the control group consumed significantly more IV fentanyl boluses intra-operatively than in the placebo (2.84 vs. 0.74, $P < 0.01$) mainly during the phase of incision and time of removal of specimen that requires bone cuts [Figure 1]. Patients in the Diclofenac Group also had better pain and sedation scores on arrival to recovery (time 0) which was statistically significant. Mean pain intensity at rest which was measured on VAS at arrival was 3.30 ± 0.65 in Placebo Group compared to 2.10 ± 0.30 in the Diclofenac Group which was significant ($P < 0.01$). Sedation scores on arrival in recovery room were 2.58 ± 0.57 and 1.66 ± 0.63 in the Placebo and Diclofenac Group, respectively ($P < 0.01$). Time to demand for first dose of analgesia in post-operative period was significantly shorter for group 1 (114.5 min vs. 252.6 min $P < 0.01$) [Figure 2].

There was no difference in pulse rate at induction, incision and removal of tumour; there was significant difference in mean arterial pressure at incision ($P < 0.01$), at primary tumour removal ($P < 0.007$) and at incision for reconstructive surgery ($P = 0.011$). None of the patients in either group required any other measures to control the BP [Figure 3].

Table 2: Demographic data

Parameter	Group I (fentanyl only)	Group II (fentanyl with diclofenac)
Age (years)	47±10	47±9
Sex (male/female)	43/7	39/11
Weight	59.00±9.767	57.00±9.203
ASA status (1/2)	38/12	36/14
Duration of anaesthesia (min)	319.10±36.710	323.40±30.109
Intra-operative blood loss (ml)	783 (300–1600)	822.4 (350–1400)

ASA – American Society of Anesthesiologists

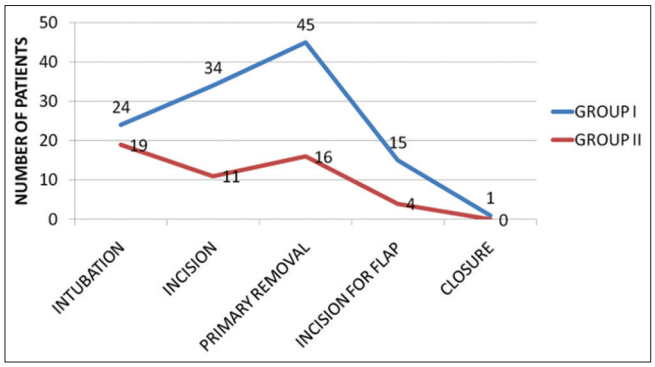

Figure 1: Comparison of number of patients requiring fentanyl boluses intra-operatively

DISCUSSION

Our study showed that diclofenac administered at the beginning of surgery reduced opioid required to control the haemodynamic response to surgical stimulation.

During balanced anaesthesia, optimum analgesia reduces the dose of anaesthetic agents and muscle relaxants resulting in a better post-operative recovery. Better analgesia also helps to maintain cardiovascular stability. Succinylcholine and vecuronium used in the study have different effects on pulse rate, but the effect is short lasting and would not affect results as interval between induction and incision usually exceeds 15 min. NSAIDs are highly effective in conditions especially where tissue inflammation contributes to pain while lacking most of the side effects of opioids. They have been used as part of pre-emptive analgesia and shown to have an opioid sparing effect in many studies in post-operative pain management.[8-10] We could not find any study on pre-emptive use of NSAIDs with opioid sparing effects in intra-operative period. There may also be benefits in cancer outcome as recent studies have shown association between use of opioids and cancer outcome.[11,12] Studies have suggested that opioid

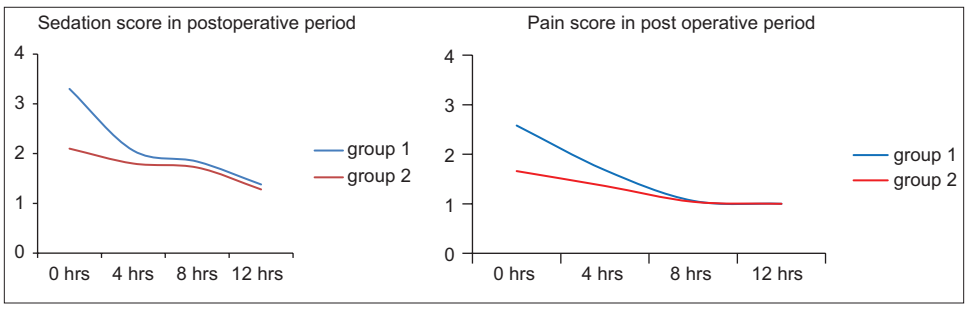

Figure 2: Comparison of pain score and sedation score in immediate post-operative period

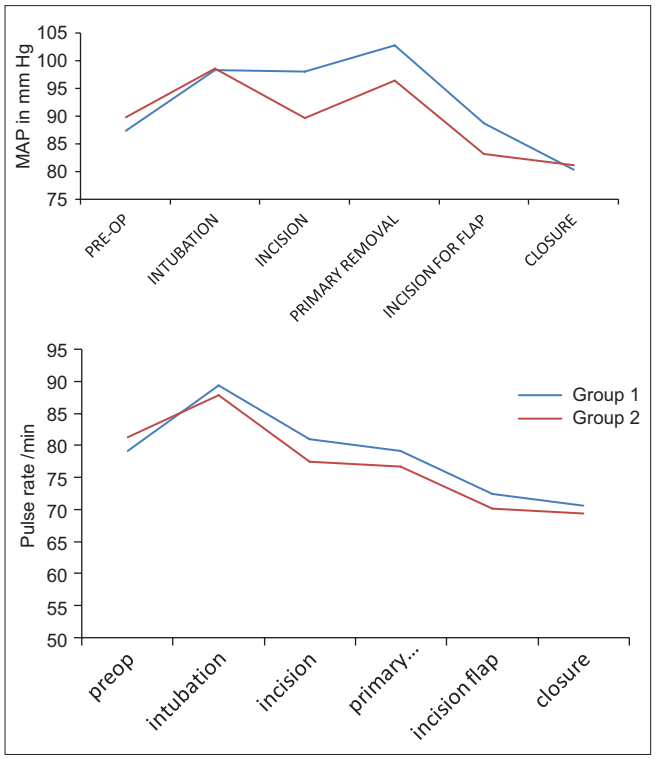

Figure 3: Comparison of mean arterial pressure and mean pulse during surgery between two groups

receptor antagonists may inhibit opiate and vascular endothelial growth factor-induced angiogenesis.[13]

The main concern is the effect of NSAIDs on platelet aggregation thereby increasing the surgical bleeding. However, studies looking for a relationship between the use of NSAIDs and perioperative bleeding have failed to show strong association. This study also did not show increased bleeding or increased need for transfusion in the Diclofenac Group. Average intra-operative blood loss in the Placebo Group was 783 ml (300–1600) compared to 822.4 ml (350–1400) ($P = 0.551$) in the Diclofenac Group.

This was a quasi-randomised study which is not ideal method of randomization. However, since surgeons were not part of this study, they were blind towards methodology. Similarly, assessors and anaesthesiologist conducting case and patient were not aware about the method of randomisation, minimizing chance of bias.

CONCLUSION

Diclofenac when given as an intra-operative analgesic reduced fentanyl consumption in the intra-operative period with extension of analgesia into the early post-operative period. Patients receiving diclofenac were significantly less sedated than those in the Placebo Group.

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Conflicts of interest

There are no conflicts of interest.

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Announcement

Conference Calender - 2015

Name of the conference: 63rd Annual National Conference of the Indian Society of Anaesthesiologists, ISACON 2015
Date: 25th to 29th December 2015
Venue: B. M. Birla Auditorium & Convention Centre, Jaipur, India
Organising Secretary: Dr. Suresh Bhargava
Contact: +91 98290 63830
E-mail: suresh3559@yahoo.com
Website: www.isacon2015jaipur.com

Name of the conference: 24th Annual State Conference of ISA AP State Chapter
Date: 30th October to 1st November 2015
Venue: Hotel Riverbay, Rajahmundry
Organising Secretaries: Dr. P. Kalyan Chakravarthy & Dr. N. V. Venugopal
Contact: +91 96427 92234 & +91 94921 00630
E-mail: isaapcon2015rajahmundry@gmail.com
Website: www.isaapcon2015.com

Name of the conference: 7th Annual Conference of ICA
Date: 13th to 15th November 2015
Venue: Hotel Savera, Dr. Radhakrishnan Road, Chennai 600004
Organising Secretary: Dr. K. Balakrishnan
Contact: +91 98410 29259
E-mail: ica2015@gmail.com (visit isaweb.in ISA > ICACON2015)

Name of the conference: UKISACON 2015: Uttrakhand State ISA Conference 2015
Date: 20th to 22nd November 2015
Venue: Max Hospital, Dehradun
Organising Secretary: Dr. Sanjeev Nivargi
Contact: +91 78959 00714
E-mail: sanjeev.nivargi@maxhealthcare.com

Name of the conference: 25th Joint Annual Conference of ISA East Zone & 36th Annual State Conference of ISA West Bengal State Branch - ISAJAC 2015
Date: 6th to 8th November 2015
Venue: Hotel The Stadel, Kolkata
Organising Chairperson: Dr. Sumanta Dasgupta, Mobile: 9002080513
Organising Secretary: Dr. Subhrndu Sarkar
Contact: +91 98311 71162
E-mail: subhendusarkar757@gmail.com
Website: www.isawb.in

Name of the conference: 8th National Conference of Paediatric Anaesthesia 2016
Date: 28th to 30th January 2016
Venue: Scudder Auditorium, Christian Medical College, Vellore
Organising Chairperson: Dr. Sajan Philip George
Organising Secretary: Dr. Ekta Rai
Contact: 0416-228-2105 / 3556
E-mail: iapa8@cmcvellore.ac.in
Website: www.ncpa2016.in

Name of the conference: 17th Annual Conference of Indian Society of Neuroanaesthesiology and Critical Care (ISNACC)
Date: 5th to 7th February 2016
Venue: NIMHANS Convention Centre, Bengaluru
Organising Chairperson: Dr. Badarinarayan V
Organising Secretary: Dr. H K Venkatesh
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E-mail: www.isnacc2016.org