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COMPARATIVE STUDY

Comparative Evaluation of Intranasal Butorphanol and Oral Diclofenac Sodium for Analgesia After Surgical Removal of Impacted Mandibular Third Molars: Split-Mouth Prospective Controlled Clinical Study

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Abstract
Aim The study intended to compare the analgesic effect and patient satisfaction of intranasal butorphanol with oral diclofenac sodium after surgical removal of impacted mandibular third molars.
Materials and Methods This split-mouth prospective controlled clinical study included 50 patients with bilateral symmetrically impacted mandibular third molars with the same difficulty on the Pederson Index. All patients had two appointments of surgery. In the first, the molar on one side was surgically removed and depending upon the chit selected by the patient, either intranasal butorphanol or oral diclofenac sodium was prescribed postoperatively for pain relief. Two weeks later, the impacted mandibular third molar on the other side was surgically removed and if butorphanol was selected for the first side, then oral diclofenac sodium was prescribed for the other side and vice versa. Pain relief was recorded on the Facial Visual Analogue Scale at 1, 2, 3, 4 and 5 h postoperatively and on postoperative day 1 and 2 at the same time for both the drugs.
Results Intensity of pain was less with intranasal butorphanol as compared to oral diclofenac sodium at all the time intervals and especially in the 1st postoperative hour. Overall acceptance (88%) to butorphanol nasal formulation was statistically similar to diclofenac sodium tablets.
Conclusion Intranasal butorphanol at the very acceptable 1 mg dose after the surgical removal of impacted mandibular third molars provides a profound degree of analgesia. It is a well-tolerated drug with a high acceptance rate if administered correctly.

Keywords Impacted mandibular molars · Intranasal drug delivery · Butorphanol nasal spray · Diclofenac sodium

Introduction

The surgical removal of impacted third molars is one of the most commonly performed procedures by an oral surgeon [1]. This is ensued by postoperative sequelae like pain, swelling and trismus. Patients often complain of pain after the effect of the local anesthetic wears off. It is thus advisable to prescribe them with a suitable analgesic in order to minimize discomfort.

Diclofenac sodium, an aryl-acetic acid derivative, is a commonly prescribed analgesic for acute postoperative pain. However, its onset of action is relatively slower with 50% pain relief over 4–6 h [2]. Moreover, oral administration may undergo hepatic first-pass metabolism making only 50–60% of the active drug available in the systemic blood stream [3, 4].

Butorphanol tartrate (BT) is an opioid analgesic which acts as an agonist-antagonist at μ and δ receptors and as a partial agonist at κ receptors [5, 6]. It has potency approximately 4 to 8 times that of morphine with a long

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duration (4–5 h) and rapid onset (5–15 min) of action accompanied by an excellent safety profile. Furthermore, it has a low dependence liability and abuse potential [7, 8].

The turn of the twentieth century spotlighted the intranasal delivery of drugs. This method of drug delivery is suitably employed for drugs that are ineffective orally, used chronically albeit in small doses and for those drugs for which rapid entry to the general circulation is desirable [9]. Butorphanol is absorbed by the oral route but undergoes hepatic first-pass metabolism, and hence, the plasma bioavailability is not sufficient from this route of delivery. For postoperative pain management, a rapid onset of action is desirable and butorphanol can be given intranasally for relieving distress rapidly. Since it is an opioid drug, there is a possibility of abuse and side effects. However, with the introduction of the nasal atomizing device, accurate required dose of BT can be appropriately administered.

In the dental setup, it was believed that the introduction of BT nasal spray has the potential to revolutionize pain management and is a promising addition to the current armamentarium of analgesics. In this study, we propose to compare patient satisfaction and its efficacy in the relief of pain after surgical removal of impacted mandibular third molars with oral diclofenac sodium.

Materials and Methods

The source of data for the study was 50 patients with bilateral symmetrically impacted mandibular third molars who had been referred to the Out-Patient Department, Department of Oral and Maxillofacial Surgery, Bharati Vidyapeeth Deemed University, Dental College and Hospital, Pune. The study was commenced after approval from the ethical review board of the institution. Written informed consent was obtained from all the individuals enrolled.

Inclusion criteria for the split-mouth prospective controlled clinical trial were patients aged between 18 and 50 years, irrespective of gender with bilateral symmetrically impacted mandibular third molars. Patients were clinically evaluated prior to selection to rule out the presence of infection and subsequently radiographically evaluated with an OPG (representative OPG Fig. 1) to ensure that the bilateral impacted mandibular third molars had the same angulation, spatial relationship, depth and consequently the same difficulty of operative procedure based on the Pederson Difficulty Index [10]. The patients selected were classified as American Society of Anesthesiologist (ASA) Physical Status 1 and were non-smokers.

Exclusion criteria:

1. Patients with clinically relevant medical problems or systemic disorders like uncontrolled diabetes mellitus, ischemic heart disease and hyperthyroidism.
2. Patients with acute nasal symptoms like common cold, flu and sinus infection
3. Patients who were allergic to the drugs employed in the study
4. Pregnant or lactating mothers
5. Individuals under intoxication of alcohol or on drug therapy (analgesics, nasal decongestants) which may confound the result or interfere with wound healing.

In the study, all patients had two appointments of surgery. In the first appointment, the impacted mandibular third molar on one side was surgically removed and depending upon the chit selected by the patient either intranasal BT (BUTRUM NS; Aristo Pharmaceuticals, Mumbai, India) or oral diclofenac sodium (VOVERAN; Novartis, Mumbai, India) was prescribed postoperatively for pain relief. If intranasal BT was prescribed, during the delivery the patient's head was tilted slightly forward and the other nostril was closed. Each actuation delivered precisely 1 mg of BT. After spraying, the patients were instructed to tilt the head backward and sniff gently to assure the proper delivery of the drug. Patient was sent home with the accompanying relative/peer. Dose was repeated every 6 h. Patient could ask for rescue medication in the form of dispersible ketorolac 10 mg if the degree of analgesia with the intranasal formulation was insufficient or if the patient experienced side effects that he/she could not tolerate.

Two weeks later, the impacted mandibular third molar on the other side was surgically removed and if BT was selected for the first side then oral diclofenac sodium (50 mg) was prescribed every 8 h for postoperative pain. The pain relief was recorded on the 10-point Facial Visual Analogue Scale (VAS: 0-no pain; 10-excessive pain) 1, 2, 3, 4 and 5 h postoperatively and at the same time on postoperative day 1 and 2. Patient satisfaction for each drug (global evaluation of drug) was assessed by a questionnaire where the patient graded the drug based on its acceptability as excellent, good, fair and poor. Data were subsequently analyzed by Mann–Whitney *U* test.

Results

Efficacy of intranasal BT in terms of pain relief at fixed stipulated time intervals and acceptance was measured against that of oral gastro-resistant diclofenac sodium. The statistically significant difference in pain (as measured with VAS) and global evaluation across two study groups (intergroup comparisons) was tested using one-tailed Mann–

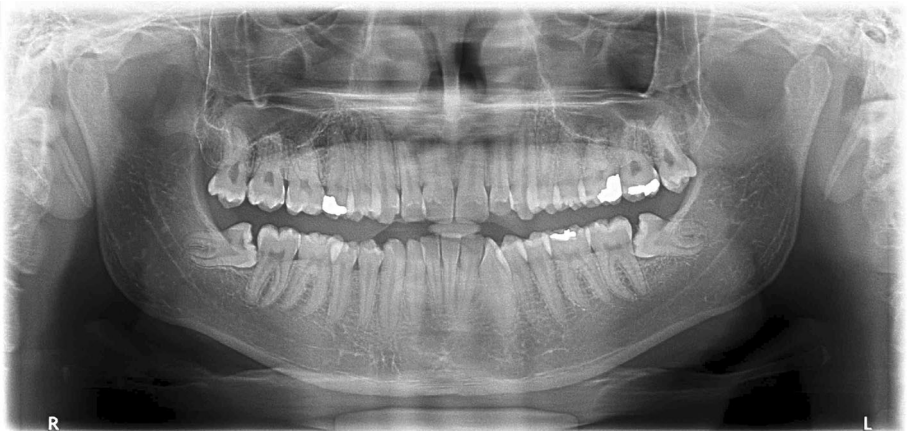

Fig. 1 Representative OPG depicting bilaterally symmetrical impacted mandibular third molars

Whitney *U* test after confirming the underlying assumptions: independent groups and ordinal data. The significance level was set at $P < 0.05$.

Table 1 depicts statistical analysis of pain for each of the drugs at fixed stipulated time intervals. *Pain relief* with BT at the 1st, 2nd, 3rd, 4th and 5th postoperative hour after the procedure was statistically superior than oral diclofenac sodium especially so in the first hour after the procedure. Perception of pain on the first and second postoperative day was significantly less with intranasal BT as opposed to oral diclofenac sodium. Figure 2 depicts a graph comparing intensity of pain (as measured with VAS) against time for nasal BT and oral diclofenac postoperatively.

Six out of the 50 patients enrolled in the study resorted to use of the rescue medication (dispersible ketorolac 10 mg), i.e., 12% of all patients from the butorphanol group. They experienced common side effects like nausea and/or dizziness and were uncomfortable with the use of the intranasal formulation. There appeared to be no statistically significant difference in the *global evaluation* of the drugs employed in the study, i.e., butorphanol nasal spray had a similar acceptance and tolerability as compared to oral diclofenac sodium. Table 2 depicts statistical analysis carried out to evaluate patient acceptance of each of the drugs. Figures 3 and 4 depict pie charts illustrating the global evaluation of intranasal butorphanol and oral diclofenac sodium, respectively.

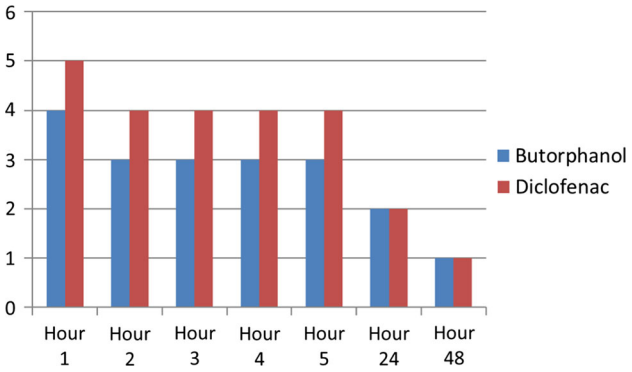

Fig. 2 Graph comparing intensity of pain (as measured with VAS) against time for nasal butorphanol and oral diclofenac postoperatively

Table 1 Statistical analysis of pain for each of the drugs at fixed stipulated time intervals

Statistical comparison of pain levels for the two drugs
Mann–Whitney *U* test (one-tailed)

Time point (h)	Median		*U*	*P* value	Conclusion
	Butorphanol (B)	Diclofenac sodium (DS)			
1	4	5	569	0.00017	Pain is less in B than DS
2	3	4	756.5	0.03129	Pain is less in B than DS
3	3	4	677	0.0048	Pain is less in B than DS
4	3	4	694.5	0.0076	Pain is less in B than DS
5	3	4	739.5	0.02168	Pain is less in B than DS
24	2	2	747.5	0.02618	Pain is less in B than DS
48	1	1	753.5	0.02354	Pain is less in B than DS

Table 2 Statistical analysis of global evaluation of patient acceptance of each drug

Statistical comparison of global evaluation for the two drugs					
	Median		*U*	*P* value	Result
	Butorphanol	Diclofenac			
Global evaluation	3	3	1204	0.3515	No statistically significant difference

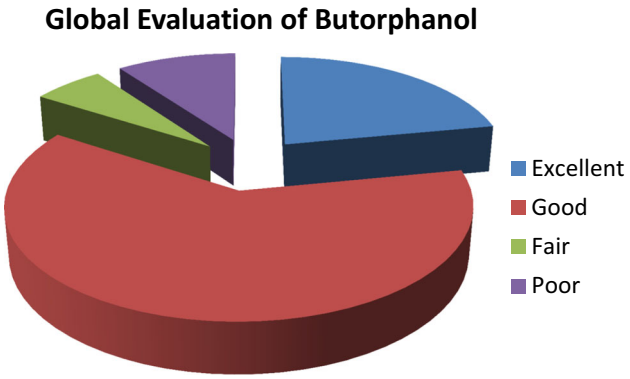

Fig. 3 Pie chart illustrating the global evaluation of intranasal butorphanol

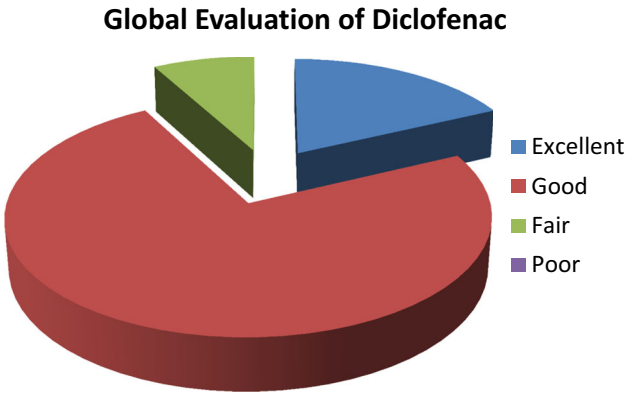

Fig. 4 Pie chart illustrating the global evaluation of oral diclofenac sodium tablets

Discussion

Pain is the most common postoperative complaint after surgical removal of impacted teeth, and this influences a patient's quality of life in the days after surgery. Minimizing postoperative pain allows patients to return to work and social activities in a shorter time. The rich vascular plexus of the nasal cavity provides a direct route for the drug molecule into the blood stream. Intranasal BT has a rapid onset of action of 15 min, peak effects within 60 min and a duration of action of 3–5 h [6, 7]. Consequently, the rates of absorption and plasma concentrations are comparable to intravenous administration and better than subcutaneous or intramuscular routes. Unlike the oral route, intranasal administration avoids low pH-associated chemical degradation, enzymatic inactivation and hepatic extraction and thus ensures excellent bioavailability.

In a study by Desjardins et al. the authors evaluated the safety and efficacy of 4 increasing doses of intranasal BT after removal of bony impacted third molars in 151 patients. The patients were randomly assigned to receive 1 dose of BT: 0.25 mg, 0.5 mg, 1.0 mg, 2.0 mg or placebo. The pain relief was rapid and as early as 15 min after administration. This concurs with our study where patients had a significant relief from pain in the 1st hour with the nasal spray compared to the oral diclofenac. The authors noted that the 1.0 and 2.0 mg groups experienced greater pain relief compared with placebo during the first hour after drug administration [11].

In a study to evaluate the efficacy and safety of trans-nasal butorphanol, Ladov et al. administered a 1 mg dose every 4 h after surgical removal of impacted third molars. However, ibuprofen (400 mg) was administered concomitantly every 4 to 6 h for the first 48 h. Butorphanol nasal spray significantly reduced the mean pain score by 50% after third molar removal within 15 min after administration, and after 30 min, mean pain was reduced by two-thirds [12]. However, since ibuprofen was administered concomitantly, a true assessment of pain relief with butorphanol only was not done in this study. The study had other limitations since it was not a randomized control trial and there was no attempt to select patients based on the type of impaction or the estimated level of anticipated postoperative pain. Somnolence, nausea and dizziness were the principal side effects in their study, but the drug via the nasal route had an overall acceptance of 82%. None of their patients rated the drug as 'poor' after the first postoperative day. This is corroborated by our study which concluded that overall acceptance in our pool of patients was 88%.

A prospective study by Scott and his associates to evaluate the efficacy of an initial 1 mg dose of trans-nasal butorphanol in different musculoskeletal injuries concluded that 93% patients received *at least* a little relief within 15 min. Seventy-one percentage of the patients received a 50% reduction of pain within 60 min. They assessed that no serious side effects were noted but drowsiness occurred in 82% of patients, dizziness in 54% and one patient discontinued the participation due to nausea [13]. Somnolence, dizziness and/or nausea were reported in 6% of our patients who consequently discontinued the drug.

A well-structured single-dose, randomized, double-blind study to evaluate the efficacy and tolerability of BT nasal spray administered via a *unit-dose device* in the management of pain after surgical removal of impacted teeth was conducted by Wermeling and his team. They compared a 1 and 2 mg dose of BT nasal spray with a placebo. Pain relief was recorded in most patients within 15 min of receiving active treatment, with the 2 mg dose of BT providing the greatest response. The nasal spray was well tolerated, with central nervous system adverse effects being most common in the active treatment groups. Dizziness occurred in 45.8% patients who received BT 1 mg, 58.3% who received BT 2 mg and 33.3% who received placebo. There were no significant changes from baseline in vital signs, pulse oximetry, nasal irritation or pathological process [8]. Their results were similar to those of previous studies of BT nasal spray administered via *multi-dose pump* for postsurgical analgesia.

It has been suggested that patient factors also have an important impact on increasing difficulty of third molar surgery, particularly age, gender, size and ethnic background, but only age has been previously linked with increased surgical time and complications [14]. The same operating surgeon carried out surgical removal of bilateral symmetrically impacted mandibular third molars within the same patient in our prospective split-mouth clinical controlled study to eliminate operator bias and bias due to patient factors. Each patient was subsequently followed up at 7 different time intervals up to postoperative day 2 for both the drugs. However, our study is not without limitations. Studies with relatively larger sample size and assessment of the drugs and their respective routes in different minor surgical procedures are imperative to corroborate our findings. Moreover, the results of our study cannot be generalized to populations other than those included in the protocol. Elderly patients may be more sensitive to the effects of BT, and patients with comorbid conditions or those taking other medications may have a different response.

Conclusion

The present study compares the efficacy and acceptance of a non-narcotic opioid delivered intranasally with oral diclofenac sodium after surgical removal of impacted mandibular third molars. Intranasal butorphanol at the very acceptable 1 mg dose repeated every 6 h after the surgery provides a profound degree of analgesia.

Further studies with a relatively larger sample size are imperative to corroborate the use of butorphanol intranasally, but within the framework of our study it appears to be a well-tolerated analgesic with a rapid onset of action *if administered correctly.* The intranasal administration of analgesics is a promising parenteral alternative. This delivery of therapeutics is an exciting area of pharmaceutics that is undergoing a renaissance.

Compliance with Ethical Standards

Conflict of interest Authors Yash Pankaj Merchant, Rajshekhar Halli and Husain Mograwala declare that they have no conflict of interest.

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