

Pain Control by Novel Route of Gifted Choice Against Peroral Route

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Received: 26 May 2016 / Accepted: 14 February 2017 / Published online: 4 March 2017
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Abstract

Introduction Pain after surgical extraction of third molars has been a nemesis for oral surgeons with clinicians, thus striving for an analgesic modality. NSAIDs are among the most widely used therapeutic classes of analgesics. Transbuccal diclofenac sodium patches have been developed as an innovative drug delivery system using buccal mucosa as a gifted choice, hence overcoming first pass metabolism and offering the advantage of sustained drug delivery with reduced incidence of systemic adverse effects.

Aim A comparative study was conducted to evaluate the efficacy of diclofenac sodium for pain control, administered via the far-fetched and gifted novel route through the transbuccal patch and by ever popular per oral route and also to assess the adverse effects vis-à-vis for transbuccal diclofenac patch and oral diclofenac following extraction of bilaterally symmetrical impacted mandibular third molars under local anaesthesia.

Methodology Thirty healthy subjects of both the sexes in the age of 12 to 50 years with asymptomatic bilaterally symmetrical mandibular third molars underwent extraction under LA. It is a split-mouth study, i.e. after the extraction of tooth on one side, diclofenac sodium (50 mg) via oral route was given and then in another visit, when the same

patient is comfortable and asymptomatic, extraction on contralateral side was executed and transbuccal patched diclofenac sodium (20 mg) was applied. Pain was measured on visual analog scale and verbal rating scale by the patient for 3 days and adverse effects if any were noted.

Result Statistical analysis showed that transbuccal diclofenac sodium was significantly efficacious when compared to the drug administered orally. Also, statistically significant results were obtained in percentage reduction in pain from 1st to 3rd postoperative day in transbuccal group. No significant difference is seen for adverse reactions.

Conclusion Transbuccal diclofenac sodium patch is more efficacious and can be used for pain control.

Keywords Pain control · Transbuccal administration · NSAIDs · Diclofenac sodium · Hydroxypropyl methyl cellulose patch · Impacted mandibular third molars

Abbreviations

TBDP	Transbuccal diclofenac patch
VAS	Visual analog scale
VRS	Verbal rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
HPMC	Hydroxypropyl methylcellulose

Introduction

In conventional oral surgical practice, extraction of impacted third molars sums up for the majority of cases and the commencement of successful treatment necessitates thorough planning and surgical dexterity both during preoperative diagnosis and postoperative management [1].

Generally, the surgical removal of mandibular third molars is preceded by patient's denunciation regarding

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pain, swelling and trismus. Postextraction pain is a torment for oral surgeons and thus seeking for a modality that would provide best analgesia without any side effects, hence fortifying patient compliance. Before the development of significant pain, treating the patient is a more humane and sophisticated perspective towards patient care and it withstands the current trends towards more combative, preventive and systematic approaches for pain control. The perception of pain is altered and hyperalgesia may occur, once nociception is upregulated both through central and peripheral mechanisms. However, this upregulation of the nociceptive system within the central nervous system can be ceased by rapid analgesic administration [2].

Patients undergoing extraction of bilaterally symmetrical impacted third molars are regarded as standardized model to evaluate acute surgical pain, as they act as self-controls with cross-over trials, and moreover, it provides a chance to perform two similar surgical procedures on separate occasions [3].

To relieve mild to moderate postoperative pain caused by third molar surgery, non-steroidal anti-inflammatory drugs (NSAIDs) work well among analgesics [4]. Diclofenac sodium which exhibits anti-inflammatory and analgesic activity is a commonly prescribed NSAID. However, due to the first pass metabolism only about 50% of the absorbed diclofenac becomes systemically accessible when administered through oral route. Furthermore, due to the elevated plasma concentration attained [5, 6], oral diclofenac also carries the probability for significant adverse reactions, particularly of the gastrointestinal tract [7–9].

Transbuccal patches have evolved as an avant-garde topical drug delivery system for diclofenac and other NSAIDs, contributing the benefits of sustained drug delivery [10] with diminished incidence of adverse systemic effects due to reduced plasma concentrations, superior patient acceptance and lower dosages [11–13].

So the expectation of limiting gastric irritation by using topical formulations and thereby avoiding the oral route is appealing, but the question of efficacy still looms large. The purpose of this study was to compare the efficacy of transbuccal diclofenac sodium patch (TBDP) with oral diclofenac sodium for pain relief following extractions in bilaterally symmetrical mandibular third molars.

Materials and Methods

Thirty healthy subjects belonging to both the genders in the age group of 12–50 years without any systemic diseases or previous drug allergy, and presented with bilaterally symmetrical, asymptomatic, impacted mandibular third molars, were included in our study.

A written informed consent was obtained from all the patients along with their respective preoperative radiographs and to publish clinical photographs. Standardization was maintained by either removing both the teeth in the same patient in toto, or both the teeth were sectioned and removed.

According to both the modes of diclofenac sodium drug administration, each patient was categorized into two groups in our split mouth study:

Group A—diclofenac sodium administered via transbuccal patch

Group B—diclofenac sodium administered via peroral route

An ethical approval was given by the Member Secretary, Institutional Ethical Committee, Sudha Rustagi College of Dental Sciences and Research, Faridabad, affiliated to Pt. B.D. Sharma University of Health and Sciences, Rohtak, which is recognized by the Dental Council of India and Ministry of Health and Family Welfare, Govt. of India.

Following removal of the impacted mandibular third molars, hydroxypropyl methylcellulose (HPMC) patch loaded with diclofenac sodium (20 mg) was placed on the buccal mucosa and given thrice a day for 3 days (Fig. 1), and amoxicillin + clavulanic acid (625 mg) was given thrice a day for 5 days. When the same patient was comfortable and returned back for extraction of mandibular third molar on the contralateral side, patient was given oral dose of diclofenac sodium (50 mg) thrice a day for 3 days and amoxicillin + clavulanic acid (625 mg) thrice a day for 5 days postoperatively.

The drugs used in our study were administered to the patient 45 min after extraction. Patient was told not to drink and eat for 1.5 h after the application of the patch on the buccal mucosa, and further the patient was asked to assign scores for a total of 72 h postoperatively at a regular

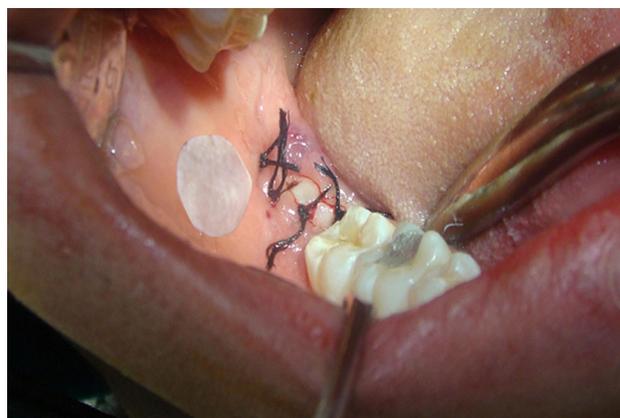


Fig. 1 Application of transbuccal diclofenac sodium HPMC patch post-surgical extraction of impacted mandibular third molar followed by suturing

interval of 8 h on visual analog scale (VAS) and verbal rating scale (VRS).

Transbuccal Patch

TBDP is one of the few drugs given via the novel route, i.e. administration via buccal mucosa.

In this patch, 20 mg diclofenac sodium is sandwiched between the two polymer layers of HPMC. The thickness of the patch is 0.308 ± 0.049 mm, shape is circular with a diameter of 1.5 cm, and colour of the patch is off white, packaged in foil-lined packets. It is used to relieve mild to moderate postoperative pain. It is applied on the buccal mucosa with a dry finger, and thereafter, digital pressure is applied over the patch for 30 s and the patch adheres to the buccal mucosa.

Mechanism of Action

This controlled drug delivery system using transbuccal patch is hinged upon the principle of mucoadhesion. Mucoadhesion is defined as a state in which two components, of which one is of biological source, are joined together for prolonged periods of time by the aid of interfacial forces. In the formulation of oral controlled release dosage forms, significant benefits may follow from the use of mucoadhesive polymers, providing brief benefits between the drug delivery system and the mucous or epithelial cell surfaces of the alimentary canal. The bond between polymers and the mucous membrane involves secondary forces, such as the Van der Waals forces. Mucoadhesives thus may be regarded as a specific class of bioadhesives.

Mucoadhesion is a complex process involving wetting, adsorption and interpenetration of polymer chains. It is established in the following stages [14]:

1. Contact stage: intimate physical contact between a bioadhesive/mucoadhesive material and a membrane (wetting or swelling phenomenon)
2. Consolidation stage: penetration of bioadhesive and mucoadhesive into the underlying tissues or into the surface of the mucous membrane (interpenetration)

Statistical Analysis

The data obtained in our study were analysed using Statistical Package for Social Sciences (SPSS) version 21. A continuous variable like age was summarized as mean and standard deviation. A categorical variable like adverse effects was summarized as frequencies. The outcome variables, i.e. VAS and VRS scores, were also summarized as mean and standard deviation. As VAS and VRS scores

Table 1 Gender and age distribution of patients

Sex	N (%)	Age (years)	
		Mean	SD
Males	12 (40)	29.83	8.19
Females	18 (60)	29.22	10.03
<i>p</i> ^a Value, significance		0.175, NS	

NS non-significant, S significant

^a Wilcoxon Signed ranks test

Table 2 Mean pain scores of 1st, 2nd and 3rd postoperative days on VAS

Group	VAS 1st day		VAS 2nd day		VAS 3rd day		
	Mean	SD	Mean	SD	Mean	SD	
Group A	2.98	1.27	2.00	1.01	0.90	0.58	
Group B	3.50	1.41	2.44	1.16	1.24	0.63	
<i>p</i> ^a Value, significance		<0.001, S		<0.001, S		<0.001, S	

Bold indicates the *p* values which are statistically significant, as the level of statistical significance was set at 0.05

^a Wilcoxon Signed ranks test

Table 3 Mean pain scores of 1st, 2nd and 3rd postoperative days on VRS

Group	VRS 1st day		VRS 2nd day		VRS 3rd day		
	Mean	SD	Mean	SD	Mean	SD	
Group A	1.39	0.35	1.03	0.39	0.37	0.20	
Group B	1.61	0.34	1.30	0.42	0.64	0.19	
<i>p</i> ^a Value, significance		<0.001, S		<0.001, S		<0.001, S	

Bold indicates the *p* values which are statistically significant, as the level of statistical significance was set at 0.05

^a Wilcoxon Signed ranks test

were ordinal variables, inferential statistics was done by nonparametric tests, i.e. Wilcoxon signed rank test, Friedman test and Mc Nemar test. The level of statistical significance was set at 0.05.

Results and Observations

Thirty healthy patients in the mean age group of 12–50 years were considered in the study undertaken. Among them, 12 were males (40%) and 18 were females (60%) (Table 1). A descriptive analysis was carried out with mean and standard deviation being computed. Wilcoxon signed rank test, Friedman test and Mc Nemar test were used to find the significance of VAS, VRS, percentage pain reduction and adverse effects between the two drug delivery systems.

Table 4 Percentage pain reduction in VAS from 1st to 2nd postoperative day and from 1st to 3rd postoperative day in group A and group B

Group	Percent reduction in VAS from 1st to 2nd day		Percent reduction in VAS from 1st to 3rd day	
	Mean	SD	Mean	SD
Group A	32.69	15.66	71.00	9.63
Group B	28.69	16.99	63.36	13.62
p^a Value, significance	0.136, NS		0.004, S	

Bold indicates the p value which is statistically significant, as the level of statistical significance was set at 0.05

^a Wilcoxon Signed ranks test

Table 5 Percentage pain reduction in VRS from 1st to 2nd postoperative day and from 1st to 3rd postoperative day in group A and group B

Group	Percent reduction in VRS from 1st to 2nd day		Percent reduction in VRS from 1st to 3rd day	
	Mean	SD	Mean	SD
Group A	26.06	23.77	74.78	13.37
Group B	19.12	20.83	59.33	11.63
p^a Value, significance	0.161, NS		<0.001, S	

Bold indicates the p value which is statistically significant, as the level of statistical significance was set at 0.05

^a Wilcoxon Signed ranks test

Table 6 Comparison of the adverse effects of diclofenac sodium in transbuccal vis-à-vis in per oral route

Adverse reactions	Frequency	Percentage
Group A	1	3.3
Group B	3	10
p^d Value	0.625, NS	

^d McNemar test

Based on the statistical data for both VAS and VRS, the p value suggested significantly better pain relief on transbuccal administration compared to per oral drug delivery at 1st, 2nd and 3rd postoperative days ($p < 0.001$). Pain scores obtained from the 1st postoperative day is the mean of 8th, 16th and 24th hours and simultaneously for 2nd and 3rd postoperative day, i.e. mean of 32nd, 40th and 48th hours and 56th, 64th and 72nd hours, respectively (Tables 2, 3).

Based upon the statistical data for percentage pain reduction in VAS and VRS from 1st to 2nd postoperative day and from 1st to 3rd postoperative day, the results are statistically significant in percentage pain reduction in 1st to 3rd postoperative day ($p = 0.004$), while in 1st to 2nd postoperative day the results were non-significant (Tables 4, 5).

On comparing the adverse effects of diclofenac sodium in transbuccal vis-à-vis in peroral route, it was observed that in group A only 1 out of the 30 patients (3.3%) had local irritation on the buccal mucosa at the site of the application of the patch, while in group B 3 out of the 30 patients (10%) suffered from GIT disturbances. So, the results came out to be non-significant with $p = 0.625$ (Table 6).

Discussion

Dental pain is rather an inexorable perception that often torments both the dentist and the patient. Hence, adequate pain control and assurance is of utmost importance during and following an intensive dental procedure, to sustain a good rapport with the patient.

Impacted mandibular third molar extraction is an exemplary model for analysing the pattern of acute dental pain. It is well established that post-extraction of impacted mandibular third molar, pain is of short period, although maximum intensity is attained in the advanced postoperative period which discourages several patients from visiting the oral surgeon [15]. So, its regulation elucidates a surgeon's clinical calibre and acumen.

Analgesics and anti-inflammatory agents play a crucial role in pain management. Post-surgical pain control in perambulant patients is best mastered by an orally effective medication having rapid onset and minimal side effects. The inflammatory origin of post-surgical dental pain has made it feasible to investigate and evaluate the analgesic effects of NSAIDs. In the current scenario with the advent of many approaches to nullify the toxicity, emergence of a novel drug administration mechanism is being encouraged. Henceforth, a clinical trial is reasonable if the newer drug delivery system is shown to be potentially less toxic without remarkable diminution in its therapeutic efficacy. Moreover, there is a growing need for such clinical models which meticulously reflect the efficacy of the present drug delivery systems and therefore bilaterally symmetrical impacted mandibular third molars were considered a purposeful mode of comparison.

Among the world of NSAIDs, diclofenac is one such drug that is profoundly used in dentistry and oral surgery for postoperative pain control in the form of tablets, suppositories and parenteral preparations. Of the various routes of drug administration, oral route is undoubtedly the most preferred by patients and clinicians alike.

However, the drawbacks accounted with the peroral drug delivery are first pass metabolism and enzymatic degradation within the gastrointestinal tract (GIT). It has been noted that small GIT ulcers and erosions are often a clinical problem with 10–30% endoscopic prevalence among patients undertaking NSAIDs [16]. Incidence of new ulcers may range from 10 to 40% of gastric ulcers and 5–15% duodenal ulcers. Also, at least 10–20% patients develop dyspepsia while on NSAIDs [17]. According to the investigations by Kappus, Serrigo and Tolmann, there were reports that higher doses and chronic usage of diclofenac induced hepatotoxic and nephrotoxic effects in human and animal experiments both [18–20]. Thus, the seriousness of GIT toxicity related to acute use of non-selective NSAIDs like diclofenac sodium can in no way be ignored.

So, the potential to make an influence in the toxicity profile of this valuable class of NSAID has served as an incentive for exploring other unconventional routes for the delivery of such drugs. And, the pursuit for substitute modes of drug deliveries to the ever popular oral route has guided for the expedition of the various novel routes. The novel routes of drug administration enhance the drug bioavailability to the surgical site which otherwise was impaired by the narrow absorption window within GIT. Transdermal analgesic patches have been routinely used in several other medical fraternities for a remarkable timespan, but drug administration via the buccal route utilizing bioadhesive dosage forms has proposed a far better drug delivery route.

Transbuccal route of drug delivery has presented distinct benefits over peroral administration for systemic drug delivery. First advantage is the exclusion of first pass metabolism, thereby preventing pre-systemic drug withdrawal within the GIT. Second is the permeability features of the site. Since it is relatively permeable, this system is more favourable for sustained drug release formulation. Thirdly, the mucosa is generously bestowed with blood vessels and is sturdy, and hence it displays brief recovery times following damage or stress. Fourthly, the buccal mucosa is comparatively immobile together with a stretch of smooth muscles making it an appealing area for retention of oral transmucosal drug delivery systems. Fifthly, due to virtual scarcity of langerhans cells buccal mucosa probably becomes more enduring to potential allergens. Further, it has many additional benefits like painless drug delivery, low enzymatic activity, easy drug withdrawal and versatility in unidirectional and multidirectional designed

local and systemic drug release systems and last but not least it can also be administered to unconscious patients [21].

In this manner, the transbuccal route for diclofenac was thought to be an ingenious delivery technique substituting oral and other conventional forms of drug administration.

It was observed from the patients in our study that the mean pain scores of VAS on the 1st, 2nd and 3rd postoperative days were comparatively less in group A, i.e. the patients on transbuccal diclofenac sodium, when compared to the patients in group B, i.e. the patients on peroral diclofenac sodium. The results were statistically significant ($p < 0.001$). Similar results were seen when both the groups were compared on the VRS, which again was found to be statistically significant ($p < 0.001$).

It has been acquainted that pain caused by third molar surgery usually begins after anaesthesia subsides and reaches its peak levels 12 h postoperatively and lasts up to the 3rd postoperative day [22, 23]. In our study, we compared the percentage reduction in pain on VAS and VRS on 1st, 2nd and 3rd postoperative days in group A and group B. Although the mean pain scores obtained affirmed that there was percentage pain reduction in VAS and VRS from 1st to 2nd postoperative day and from 1st to 3rd postoperative day in both the groups, the statistically significant results were observed in the percentage pain reduction from 1st to 3rd postoperative day on VAS and VRS only in group A when compared with group B, with p value being 0.004 and <0.001 , respectively. Thus, our study proclaims that with transbuccal diclofenac sodium there is better percentage reduction in pain from 1st to 3rd postoperative day.

When considering the safety, 20 mg diclofenac sodium patch was well tolerated, but only 1 out of 30 patients (3.3%) reported mild irritation on the buccal mucosa, which was due to patient's repeated application of transbuccal patch on the same site. On the contrary, in the 50 mg diclofenac sodium peroral group 3 out of 30 patients (10%) reported gastric irritation.

Conclusively, TBDP patch can play a crucial role in pain control following minor oral surgical procedures including surgical extraction of impacted mandibular third molars, especially in the patients who are susceptible to gastritis and in whom compliance is a problem.

Perhaps, this route of drug delivery could alleviate the pain of various other origins in the maxillofacial region like in temporo-mandibular joint disorder, postoperative locoregional pain, and post-ablative pain by enhancing strength of the analgesic drug in the transbuccal patch.

The shortcomings of our study can be attributed to a small sample size, due to which the results obtained are not sagaciously inferring about the various adverse reactions associated with peroral route and novel route of drug

administration. So, a larger sample size is needed to appreciably corroborate the efficacy of this diacritic gifted choice of drug delivery route, i.e. the transbuccal route.

Acknowledgements We would like to show our gratitude to Sudha Rustagi College of Dental Sciences and Research, Faridabad, for sharing its pearls of wisdom with us during the course of this research. We are also immensely grateful to Dr K R Indushekar, Member secretary, Institutional Ethical Committee, who provided insight and expertise that greatly assisted the study.

Compliance with Ethical Standards

Conflict of interest Authors Dr. Kartikeya Sharma, Dr. Pallavi Sharma, Dr. Ashish Gupta, Dr. Pankaj Bansal and Dr. Shivprasad Behera declare that they have no conflict of interest.

Ethical Approval All procedures performed in the study involving human participants were in accordance with the ethical standards approved by the Member Secretary, Institutional Ethical Committee, Sudha Rustagi College of Dental Sciences and Research, Faridabad, affiliated to Pt. B.D. Sharma University of Health and Sciences, Rohtak, which is recognized by the Dental Council of India and Ministry of Health and Family Welfare, Govt. of India.

Informed Consent Informed consent was obtained from all individual participants included in the study.

References

- Susarla MS, Dodson TD (2004) Risk factors for third molar extraction difficulty. *J Oral Maxillofac Surg* 62:1363–1371
- Desjardins PJ, Grossman EH, Kuss ME, Talwalker S, Dhadda S, Baum D, Hubbard RC (2001) The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. *Anesth Analg* 93:721–727
- Baichali PS, Nandakumar H (2009) Comparative study of diclofenac transdermal patch against oral diclofenac for pain control following removal of mandibular impacted third molars. *J Oral Maxillofac Surg* 8(2):167–172
- Cooper SA, Beaver WT (1976) A model to evaluate mild analgesics in oral surgery out patients. *Clin Pharmacol Ther* 20:241
- The royal college of anaesthetists. Guidelines for the use of Non steroidal anti-inflammatory drugs in the perioperative period. March 1998
- Heyneman CA, Lawless-Liday C, Wall GC (2000) Oral versus topical NSAIDs in rheumatic diseases. A Comparison. *Drugs* 60:555–574
- Dhikav V, Singh S, Pande S, Chawla A, Anand KS (2003) Non-steroidal drug-induced gastrointestinal toxicity: mechanism and management. *J Indian Acad Clin Med* 4(4):315–322
- Naesdal J, Brown K (2006) NSAIDs associated adverse effects and acid control aids to prevent them a review of current treatment options. *Drugs Saf* 29:119–132
- Roth SH, Shainhouse JZ (2004) Efficacy and safety of topical diclofenac sodium (Pennsaid) in the treatment of primary osteoarthritis of the knee: a randomized, double-blind, vehicle controlled clinical trial. *Arch Intern Med* 164:2017–2023
- Doshi A, Koliyote S, Joshi B (2011) Design and evaluation of buccal film of diclofenac sodium. *Int J Pharm Biol Sci* 1(1):17–30
- Predel HG, Kroll R, Pabst H, Dieter R, Gallacchi G, Gianetti B et al (2004) Diclofenac patch for topical treatment of acute impact injuries: a randomized, double blind, placebo controlled, multicentre study. *Br J Sports Med* 38:318–323
- Cranny A, O’Donnell S (2005) Topical diclofenac improved pain and physical functions with no systemic side effects in primary osteoarthritis of the knee. *Evid Based Med* 10:81
- Radbruch L (2003) Buprenorphin TDS used in daily practice, benefits for patients. *Int J Clin Pract Suppl* 133:19–22
- Khan AB, Mahamana R, Pal E (2014) Review on mucoadhesive drug delivery system: novel approach in modern era. *J Pharm Sci* 4(4):128–141
- Shugars DA, Benson K, White RP, Simpson KN, Bader JD (1996) Developing a measure of patient perceptions of short-term outcomes of third molar surgery. *J Oral Maxillofac Surg* 54(12):1402–1408
- Wolfe MM, Lichtenstein DR, Singh G (1999) Gastrointestinal toxicity of non steroidal anti inflammatory drugs. *New Engl J Med* 340:1888–1899
- Doomra R, Gupta SK (2001) Intensive adverse drug reaction monitoring in various specialty clinics of a tertiary care hospital in North India. *Int J Med Toxicol* 4(1):1–4
- Simon LS, Weaver AL, Graham DY (1999) Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 282(20):1921–1928
- Tolman KG (1998) Hepatotoxicity of non-narcotic analgesics. *Am J Med* 105(1B):13S–19S
- Kappus H (1986) Overview of enzyme systems involved in bioreduction of drugs and in redox cycling. *Biochem Pharm* 35:1–6
- Uyemura SA, Santos AC, Mingatto FE, Jordani MC, Curti C (1997) Diclofenac sodium and mefenamic acid: potent inducers of the membrane permeability transition in renal cortex mitochondria. *Arch Biochem Biophys* 342(2):231–235
- Susarla MS, Blaeser BF (2003) Third molar surgery and associated complications. *Oral Maxillofac Surg Clin North Am* 15:177–186
- Varghese KG (2010) A practical guide to the management of impacted teeth, 1st ed, p136