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The Use of Ibuprofen in the Treatment of Postoperative Pain in Dentistry

Aleksandar Jakovljević[1], Emira Lazić[2], Neda Perunović[3], Nenad Nedeljković[2]

[1]Department of Oral Surgery and Implantology, School of Dental Medicine, University of Belgrade, Belgrade, Serbia;
[2]Department of Orthodontics, School of Dental Medicine, University of Belgrade, Belgrade, Serbia;
[3]Department of Periodontics and Oral Medicine, School of Dental Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Postoperative pain is common complication after daily dental care. Non-steroidal anti-inflammatory drugs are among most widely prescribed analgesics for management of postoperative pain. The analgesic effect of a non-steroidal anti-inflammatory drug (NSAID) is related to its ability to inhibit prostaglandin synthesis. Ibuprofen (2-proprionic acid derivate) was discovered in the 1960s as a representative of NSAIDs. It is a peripherally acting analgesic with a potent anti-inflammatory action. An extensive retrospective analysis of randomized clinical trials conducted over the last 40 years demonstrated that ibuprofen is effective in moderate to severe postoperative pain for different indications in dentistry. In comparison to other NSAIDs, ibuprofen is characterized by its efficiency, safety and good tolerance. The aim of this article was to present the most important pharmacological and therapeutic characteristics and side effects of ibuprofen used for postoperative pain treatment in dentistry.

Keywords: postoperative pain; non-steroid anti-inflammatory drugs; ibuprofen

INTRODUCTION

Pain represents an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]. Like all sensory experiences, pain has two components. The first component is the awareness of a painful stimulus and the second is emotional effect evoked by this experience [2]. Pain is provoked when a variety of inflammatory mediators (bradykinin, histamine, leukotrienes, and prostaglandin E2) are released into the tissues. These pain-inducing substances can be produced and released from different immune cells by trauma, infection, and allergenic reactions [3]. Acute pain is the most common complaint that causes patients to seek help from healthcare professionals. Patients typically associate dental care with pain [4, 5]. Furthermore, the postoperative pain is one of the most frequent complaints and influences patients' quality of life in the days following surgery [6].

There are three pharmacological approaches for the management of postoperative pain: a) drugs that block inflammatory mediators that sensitize or activate pulpal nociceptors; b) drugs that block the propagation of impulses along the peripheral nerves; and c) drugs that block central mechanisms of pain perception and hyperalgesia [7]. Analgesics are classified as opioids and non-opioids. Endogenous opioid peptides, opium alkaloids, half synthetic and synthetic opioids are opioid analgesics. The non-opioid analgesics include acetaminophen (APAP) and the nonsteroidal anti-inflammatory drugs (NSAIDs) [8]. NSAIDs are among the most widely prescribed analgesics for management of postoperative pain [9].

The analgesic effect of a NSAID is related to its ability to inhibit prostaglandin synthesis. NSAIDs block prostaglandin production by the inhibition of the cyclooxygenase (COX). COX is an enzyme that catalyzes the conversion of arachidonic acid, an essential fatty acid present in cell membrane phospholipids, into prostaglandins (PGs) and prostanoids. Two forms of COX isoenzymes have been identified. The constitutive form (COX-1) is present in most tissues (the gastrointestinal (GI) tract, kidneys, and platelets) with a protective role. The inducible form (COX-2) is expressed in normal tissues at low levels and is highly induced by pro-inflammatory mediators in the setting of inflammation, injury, and pain. Most NSAIDs are nonselective and inhibit both COX-1 and COX-2 families. The anti-inflammatory benefits of these drugs are primarily derived from COX-2 inhibition, while inhibition of COX-1 often elicits various side effects [8, 10].

Ibuprofen is a 2-proprionic acid derivate discovered in the 1960s. Ibuprofen is a peripherally acting analgesic with a potent anti-inflammatory action [11]. It is non selective inhibitor of cyclooxygenase (COX-1 and COX-2) [12]. This analgesic was developed directly as a result of the problems associated with the use of corticosteroids in the treatment of rheumatoid arthritis and also because of the side effects of the established NSAIDs, at that time [13].

The aim of this paper was to present pharmacological and therapeutic features and side effects of ibuprofen used for postoperative pain treatment in dentistry.

Address for correspondence: Aleksandar JAKOVLJEVIĆ, Department of Oral Surgery and Implantology, School of Dental Medicine, University of Belgrade, Dr Subotća 4, 11000 Belgrade, Serbia; *dr.sasuli@hotmail.com*

PHARAMACOLOGICAL CHARACTERISTICS OF IBUPROFEN

Ibuprofen is chiral and it is administrated clinically as a racemic mixture of both R (-) and S (+) enantiomers. The S (+) enantiomer of ibuprofen possesses the majority of pharmacological activity. It has been reported that it is about 160 times more potent than R (-) form of ibuprofen in inhibiting prostaglandin synthesis *in vitro*. Additionally, 50-60% of the R (-) form of ibuprofen is metabolically converted to the S (+) form into the intestinal tract and liver after oral absorption [14, 15, 16].

For routine clinical use, the oral route is mostly used for administration of ibuprofen. Beside the oral route, it has also been administered topically, intraocularly, intravenously, intramuscularly and rectally. Usual oral doses of 1.2-1.8 g daily are administrated in divided doses for adult patients (up to a maximum of 2.4 g per day). In children, usual doses of 20-40 mg/kg may be given as divided oral doses [17]. The absorption of ibuprofen is rapid and complete when given orally. A soluble granular form of ibuprofen demonstrates quicker absorption and a significantly higher plasma concentrations compared with tablet preparations (t_{max}<0.25 hours for granules and about 2 hours for tablets).

Similarly to other NSAIDs, ibuprofen displays extensive (99%) binding to plasma proteins [18]. Consequently, ibuprofen is characterized with low volume of distribution (10 to 15 L for an individual weighing 70 kg), small values for total body clearance (0.01 to 0.05 L/kg/min) and short half-life (2.1 hours) [19]. Ibuprofen is extensively metabolized in the liver through cytochrome enzymes P450 2C9, CYP-2C8 and 2C19. A major metabolic pathway of ibuprofen is conjugation with glucuronic acid to yield acyl glucuronides. The excretion of drug and metabolites occurs rapidly in both urine and faeces. Ibuprofen is eliminated following biotransformation to glucuronide conjugate metabolites that are excreted in urine, with little of the drug being eliminated unchanged. The excretion of conjugates may be tied to renal function and the accumulation of conjugates occurs in end-stage renal disease. Various hepatic diseases and cystic fibrosis can alter the disposition kinetics of ibuprofen [18-21].

CLINICAL IMPLICATIONS OF IBUPROFEN USE IN DIFFERENT FIELDS OF DENTISTRY

An extensive retrospective analysis of randomized clinical trials conducted over the last 40 years demonstrated that ibuprofen is effective in the treatment of moderate to severe postoperative pain in different fields of dentistry [22]. The ibuprofen efficiency in postoperative pain treatment is evident in its use after oral surgical procedures. The use of NSAIDs after oral surgical procedures is well documented in the literature. Oral surgical procedures can vary in difficulty and the degree of tissue trauma. Greater the amount of tissue injury leads to an increased amount of inflammation in the perisurgical area (pain, edema, erythema, and loss of function) that commonly occur after difficult surgical procedure.

Third molar removal is one of the most common surgical procedures carried out in daily dental practice [23]. The first study that reported the efficacy of ibuprofen after third molar removal was conducted by Lökken et al. [24]. They reported significant difference in the efficacy of ibuprofen for postoperative pain control in a group of 24 patients as compared to a placebo group after bilateral third molar surgery. Several studies have investigated analgesic dose-response of ibuprofen 200, 400, 600 and 800 mg on postoperative pain management after surgical removal of third molars [25, 26, 27]. It has been reported that ibuprofen 400 mg provided maximum pain relief and the longest durations of analgesic effects comparing to other doses [26, 27]. Furthermore, well-established analgesic effect of ibuprofen 400 mg was confirmed in Averbuch and Katzper's study [28], which concluded that the intensity of initial pain is not correlated to the need for larger doses of analgesic.

Seymour et al. [29, 30] compared both the speed of onset and the efficacy of analgesia produced by the soluble formulation or by the conventional-release tablet formulation of ibuprofen in patients with postoperative pain after third molar surgery. Both treatments were shown to be efficacious in treating postoperative dental pain. The soluble form was found to provide more rapid onset of analgesia than ibuprofen tablets in the first 30 minutes. These results are in accordance with the study of Sharma et al. [31], who reported that an effervescent granule formulation provided more rapid onset of analgesia and pain relief then tablet formulation of ibuprofen. This may be due to more rapid absorption with the soluble effervescent formulation, extensive binding to plasma proteins and local action of ibuprofen in solution in the mouth [29, 30, 31].

Preventive use of NSAIDs before the treatment may be more beneficial because it can potentially prevent the induction of central sensitization by blocking the arrival of nociceptive input to the central nervous system. Also, they can prevent peripheral sensitization by preventing formation of pain mediators in injured tissues [32, 33]. Dionne et al. [34, 35] evaluated analgesic effect of pre and postoperatively administered ibuprofen in patients undergoing impacted third molar removal. Preventive use of ibuprofen 400 mg resulted in delayed onset and reduced severity of postoperative pain, without an increase in side effects.

In postoperative pain treatment that occurs after oral surgical procedures ibuprofen has been more effective than aceclofenac [36] and celeoxib [37]. Furthermore, it has been reported that ibuprofen in combination with ketorolac [38] and oxycodone [39] was more effective for pain control after oral surgical procedures. However, Joshi et al. reported no significant difference in ibuprofen efficacy for postoperative pain control in comparison to diclofenac and acetaminophen with codeine [40].

NSAIDs have also been effective in postoperative pain control after periodontal surgery [41, 42, 43]. Ettlin et al. [44] reported in randomized, triple-blind, placebo-controlled trial superiority of ibuprofen over placebo for pain control during and after periodontal scaling and root planning. The authors have pointed out that evidences from animal experiments and clinical trials showed

NSAIDs mainly responsible for stabilization of periodontal conditions by reducing the rate of alveolar bone resorption [41-44]. Additionally, efficient use of ibuprofen has been confirmed in gingivitis treatment as a result of inhibition of proinflammatory mediators [45, 46].

Moreover, Salvi et al. [47] reported that effects of NSAIDs dropped off rapidly after drug withdrawal. The authors have thought that the development of topical NSAIDs formulations (e.g. gels, toothpastes, rinses) with daily application might be future perspective in resolving this issue.

Pain that occurs after the orthodontic treatment is also possible to resolve with analgesic effects of ibuprofen. Studies have shown that patients undergoing tooth movement can experience varying degrees of discomfort immediately after orthodontic treatment [48, 49]. According to pressure-tension theory, proinflammatory mediators, prostaglandin E_1 (PGE_1) and PGE_2 contribute to tooth movement. Consequently, they are involved in the mediation of orthodontic pain [50]. Several studies have shown that ibuprofen was efficient in pain control after initial orthodontic therapy. Furthermore, they have concluded that administration of ibuprofen 400 mg one hour before orthodontic treatment would suppress the onset of pain and reduce patient's discomfort as the result of inhibition of proinflammatory mediators [51, 52, 53].

The lack of profound anesthesia in teeth with inflamed pulp is a well-known clinical symptom. The inferior alveolar nerve block (IANB) is the most frequently used mandibular anesthetic technique for achieving local anesthesia. In 30–80% of patients with irreversible pulpitis single IANB is ineffective [54]. The reasons are increased resorption and decreased dissociation of anesthetic solution in acid environment and induced sensitization of peripheral nociceptors [55]. Several studies have shown that use of ibuprofen 600 mg (one hour before administration of anesthesia) significantly improved the efficacy of IANB in patients with symptomatic irreversible pulpitis [56, 57, 58]. Furthermore, Moderasi et al. [59] reported efficient use of ibuprofen 400 mg one hour before endodontic treatment as an effective method for achieving a deep anesthesia, pain decrease during and after root canal treatment and increase of patient's comfort. On the other side, few studies have failed to show the achievement of painless dental treatment and patient's comfort after use of different NSAIDs [60, 61]. In that case, as solution, Nusstein [62] proposed the use of supplemental injections (intrapulpal and periodontal ligament injections) to improve patient's comfort.

SIDE EFFECTS OF IBUPROFEN

Non-steroidal anti-inflammatory drugs are associated with a number of side effects. The most common minor side effects include nausea, vomiting, diarrhea, dizziness, and headache while serious side effects include prolonged bleeding after surgery, kidney failure, and gastrointestinal and cardiovascular adverse effects. The risk of short-term use and lower doses of most non-steroidal anti-inflammatory drugs is minimal. On the other side, prolonged duration of NSAIDs treatment (>1 year) increases the risk of serious side effects on gastrointestinal and cardiovascular systems [63].

Gastrointestinal (GI) toxicity is the most common side effect of NSAIDs. It is a consequence of nonselective inhibition of cyclooxygenase enzymes, especially COX-1 that is included in homeostatic protection of gastric mucosa. All traditional nonselective NSAIDs are associated with an increased risk of gastrointestinal complications, including gastrointestinal hemorrhage, perforation, and obstruction [64]. In general, ibuprofen has the lowest risk among the traditional NSAIDs, diclofenac and naproxen have intermediate risks, and piroxicam and ketorolac carry the greatest risk [65, 66]. GI side effects are more likely in elderly patients, patients who have a history of GI disease, patients who have concurrent *Helicobacter pylori* infection, patients using steroids or anticoagulants, and patients on higher doses of NSAIDs [67]. Several strategies may be used to reduce the risk of GI complications associated with NSAID use. They include, the use of other NSAIDs (selective COX-2 NSAIDs) when possible or the use of the lowest effective dose in short-term period with anti-ulcer co-therapy and cyclooxygenase-2 inhibitors in high-risk patients [68].

All NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocadial infarction, and stroke. $Thromboxane_{A2}$ (TX_{A2}) and prostacyclin (PGI_2) are prostanoids included in regulation of vascular tone and thrombosis. TX_{A2} is a vasoconstrictor which promotes platelet adhesion and aggregation. On the other side, PGI2 is a vasodilator with anti-aggregatory platelet functions. Platelets activity result from a balance between PGI_2 effects on endothelium and TX_{A2} effects on platelets. Platelets are especially vulnerable to COX inhibition, because they cannot regenerate this enzyme. NSAIDs may increase the risk of cardiovascular events at high doses through the activation of thrombosis via decreased PGI_2 production and permanent TX_{A2} levels [69]. Non selective NSAIDs, like COX-2 inhibitors, may also contribute to development of cardiovascular thrombotic events, myocardial infarction, and stroke [70]. On the other hand, the findings of Rahme et al. [71] suggested low risk of cardiovascular events of ibuprofen in comparison to acetaminophen, aceclofenac and celecoxibum.

Other adverse effects of NSAIDs, such as renal failure and liver toxicity have been reported less frequently. Due to constitutive expression of COX-2 in kidneys, the effects of nonselective and COX-2 selective NSAIDs on renal function, electrolyte imbalance, and peripheral edema are similar. The postulated mechanism is the inhibition of renal prostaglandins synthesis, which may be important in the autoregulation of renal blood flow. There is a risk of peripheral edema and hyperkalemia, particularly in patients who have diabetes, elderly patients, and patients on other hyperkalemia-inducing agents such as potassium-sparing diuretics or angiotensin-converting enzyme (ACE) inhibitors [69]. Several studies have described acute hepatitis and liver failure in patients receiving COX-2 inhibitors, like nimesulide [72, 73]. On the other side, hepatic reaction was rarely associated with use

of ibuprofen [74]. In summary, NSAIDs are contraindicated for patients who have current history of erosive or ulcerative conditions of GI mucosa, severe kidney, heart and liver disorders, during last trimester of pregnancy, or intolerance or allergy to any NSAID [8].

CONCLUSION

Pain treatment remains an important consideration in dental care. Ibuprofen is efficacious in postoperative pain treatment in wide spectrum of indications with regards to its efficacy, safety and good tolerance. Rational use will result in efficacious postoperative pain treatment with minimum side effects.

REFERENCES

1. Merskey H, Bogduk N. Part III: Pain Terms, A Current List with Definitions and Notes on Usage. In: Merskey H, Bogduk N, editors. IASP Task Force on Taxonomy. 2nd ed. Seattle: IASP Press; 1994. p.209-14.
2. Todorović Lj. Mogućnosti eliminacije bola. In: Todorović Lj, editor. Anestezija u stomatologiji. Beograd: Univerzitet u Beogradu; 1997. p.19-21.
3. Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011; 152:S33-40.
4. Mehlisch DR. The efficacy of combination analgesic therapy in relieving dental pain. J Am Dent Assoc. 2002; 133:861-71.
5. Watkins CA, Logan HL, Kirchner HL. Anticipated and experienced pain associated with endodontic therapy. J Am Dent Assoc. 2002; 133:45-54.
6. Savin J, Ogden GR: Third molar surgery – a preliminary report on aspects affecting quality of life in the early postoperative period. Br J Oral Maxillofac Surg. 1997; 35:246-53.
7. Hargreaves KM, Seltzer S. Pharmacological control of dental pain. In: Hargreaves KM, Goodis E, editors. Seltzer and Bender's Dental Pulp. 1st ed. Chicago: Quintessence Publishing Co.; 2002. p.205-226.
8. Becker DE. Pain management: Part 1: Managing acute and postoperative dental pain. Anesth Prog. 2010; 57:67-78.
9. Bradbury F. How important is the role of the physician in the correct use of a drug? An observational cohort study in general practice. Int J Clin Prat. 2004; 144:27-32.
10. McCracken JA. Prostaglandins and leukotrienes: locally acting agents. In: Melmed S, Conn PM editors. Endocrinology, Basic and Clinical Principles. 2nd ed. Totowa: Humana Press Inc.; 2005. p.93-112.
11. Adams SS. The propionic acids: a personal perspective. J Clin Pharmacol. 1992; 32:317-23.
12. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. Am J Med. 1998; 104:413-21.
13. Busson M. Update on ibuprofen: review article. J Int Med Res. 1986; 14:53-62.
14. Higton F. The pharmacokinetics of ibuprofen in human and animals. In: Rainsford KD, editor. Ibuprofen: A Critical Bibliographic Review. 1st ed. Philadelphia: Taylor and Francis Ldt.; 1999. p.79-131.
15. Adams SS, Bresloff P, Mason CG. Pharmacological differences between the optical isomers of ibuprofen; evidence for metabolic inversion of the (-)- isomer. J Pharm Pharmacol. 1976; 28:256-7.
16. Jamali F, Mehvar R, Russell AS, Sattari S, Yakimets WW, Koo J. Human pharmacokinetics of ibuprofen enantiomers following different doses and formulations: intestinal chiral inversion. J Pharm Sci. 1992; 81:221-5.
17. Reynolds JEF. Martindale: The Extra Pharmacopoeia. 30th ed. London: Pharmaceutical Press; 1993. p.292-314.
18. Lin JH, Cocchetto DM, Duggan DE. Protein binding as a primary determinant of the clinical pharmacokinetic properties of non-steroidal anti-inflammatory drugs. Clin Pharmacokinet. 1987; 12:402-32.
19. Davies NM. Clinical pharmacokinetics of ibuprofen. The first 30 years. Clin Pharmacokinet. 1998; 34:101-54.
20. Kepp DR, Sidelmann UG, Hansen SH. Isolation and characterization of major phase I and II metabolites of ibuprofen. Pharm Res. 1997; 14:676-80.
21. Evans AM, Nation RL, Sansom LN, Bochner F, Somogyi AA. The relationship between the pharmacokinetics of ibuprofen enantiomers and the dose of racemic ibuprofen in humans. Biopharm Drug Dispos. 1990; 11:507-18.
22. Beaver WT. Impact of non-narcotic oral analgesics on pain management. Am J Med. 1988; 84:3-15.
23. Silvestri AR Jr, Singh I. The unresolved problem of the third molar: Would people be better off without it? J Am Dent Assoc. 2003; 134:450-5.
24. Lökken P, Olsen I, Bruaset I, Norman-Pedersen K. Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: a test with ibuprofen. Eur J Clin Pharmacol. 1975; 8:209-16.
25. Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N. The correlation between blood levels of ibuprofen and clinicalanalgesic response. Clin Pharmacol Ther. 1986; 40:1-7.
26. Schou S, Nielsen H, Nattestad A, Hillerup S, Ritzau M, Branebjerg PE, et al. Analgesic dose-response relationship of ibuprofen 50, 100, 200 and 400mg after surgical removal of third molars: a single dose, randomised, placebo-controlled double-blind study of 304 patients. Clin Pharmacol. 1998; 385:447-54.
27. Derry S, Derry CJ, Moore RA. Single dose oral ibuprofen plus oxycodone for acute postoperative pain in adults. Cochrane Database Syst Rev. 2013; 26:CD010289.
28. Averbuch M, Katzper M. Severity of baseline pain and degree of analgesia in the third molar post-extraction dental pain model. Anesth Analg. 2003; 97:163-7.
29. Seymour RA, Hawkesford JE, Weldon M, Brewster D. An evaluation of different ibuprofen preparations in the control of postoperative pain after third molar surgery. Br J Clin Pharmacol. 1991; 31:83-7.
30. Seymour RA, Ward-Booth P, Kelly PJ. Evaluation of different doses of soluble ibuprofen and ibuprofen tablets in postoperative dental pain. Br J Oral Maxillofac Surg. 1996; 34:110-4.
31. Sharma NK, Kindelan JD, Hutchinson D, Lancaster L. A study to compare ibuprofen effervescent granules with ibuprofen tablets in the treatment of acute dental pain. Prim Den Care. 1994; 1:5-8.
32. Kissin I. Preemptive analgesia: problems with assessment of clinical significance. Methods Mol Biol. 2010; 617:475-82.
33. Dahl JB, Kehlet H. The value of pre-emptive analgesia in the treatment of post-operative pain. Br J Anaesth. 1993; 70:434-49.
34. Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. Oral Surg Oral Med Oral Pathol. 1978; 45:851-6.
35. Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B. Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol. 1983; 23:37-43.
36. Seymour RA, Frame J, Negus TW, Hawkesford JE, Marsden J, Matthew IR. The comparative efficacy of aceclofenac and ibuprofen in postoperative pain after third molar surgery. Br J Oral Maxillofac Surg. 1998; 36:375-9.
37. Doyle G, Jayawardena S, Ashraf E, Cooper SA. Efficacy and tolerability of nonprescription ibuprofen versus celecoxib for dental pain. J Clin Pharmacol. 2002; 42:912-9.
38. Forbes JA, Kehm CJ, Grodin CD, Beaver WT. Evaluation of ketorolac, ibuprofen, acetaminophen, and an acetaminophencodeine combination in postoperative oral surgery pain. Pharmacotherapy. 1990; 10:94S-105S.
39. Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 7.5 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, singledose, parallel-group study in a dental pain model. Clin Ther. 2005; 27:418-29.
40. Joshi A, Parara E, Macfarlane TV. A double-blind randomised controlled clinical trial of the effect of preoperative ibuprofen, diclofenac, paracetamol with codeine and placebo tablets for relief of postoperative pain after removal of impacted third molars. Br J Oral Maxillofac Surg. 2004; 42:299-306.

41. Pearlman B, Boyatzis S, Daly C, Evans R, Gouvoussis J, Highfield J, et al. The analgesic efficacy of ibuprofen in periodontal surgery: A multicentre study. Aust Dent J. 1997; 42:328-34.
42. Betancourt JW, Kupp LI, Jasper SJ, Farooqi OA. Efficacy of ibuprofen-hydrocodone for the treatment of postoperative pain after periodontal surgery. J Periodontol. 2004;75:872-6.
43. Rashwan WA.The efficacy of acetaminophen-caffeine compared to Ibuprofen in the control of postoperative pain after periodontal surgery: a crossover pilot study. J Periodontol. 2009; 80:945-52.
44. Ettlin DA, Ettlin A, Bless K, Puhan M, Bernasconi C, Tillmann HC, et al. Ibuprofen arginine for pain control during scaling and root planing: a randomized, triple-blind trial. J Clin Periodontol. 2006; 33:345-50.
45. Heasman PA, Seymour RA, Boston PF.The effect of a topical non-steroidal anti-inflammatory drug on the development of experimental gingivitis in man. J Clin Periodontol. 1989; 16:353-8.
46. Sekino S, Ramberg P, Lindhe J. The effect of systemic administration of ibuprofen in the experimental gingivitis model. J Clin Periodontol. 2005; 32:182-7.
47. Salvi GE, Lang NP. The effects of non-steroidal anti-inflammatory drugs (selective and non-selective) on the treatment of periodontal diseases. Curr Pharm Des. 2005;11:1757-69.
48. Ngan P, Kess B, Wilson S.Perception of discomfort by patients undergoing orthodontic treatment. Am J Orthod Dentofacial Orthop. 1989; 96:47-53.
49. Fernandes LM, Ogaard B, Skoglund L. Pain and discomfort experienced after placement of a conventional or a superelastic NiTi aligning archwire. A randomized clinical trial. J Orofac Orthop. 1998; 59(6):331-9.
50. Gurton AU, Akin E, Sagdic D, Olmez H. Effects of PGI2 and TxA2 analogs and inhibitors in orthodontic tooth movement. Angle Orthod. 2004; 74:526-32.
51. Ngan P, Wilson S, Shanfeld J, Amini H. The effect of ibuprofen on the level of discomfort in patients undergoing orthodontic treatment. Am J Orthod Dentofacial Orthop. 1994; 106:88-95.
52. Salmassian R, Oesterle LJ, Shellhart WC, Newman SM. Comparison of the efficacy of ibuprofen and acetaminophen in controlling pain after orthodontic tooth movement. Am J Orthod Dentofacial Orthop. 2009; 135:516-21.
53. Bradley RL, Ellis PE, Thomas P, Bellis H, Ireland AJ, Sandy JR. A randomized clinical trial comparing the efficacy of ibuprofen and paracetamol in the control of orthodontic pain. Am J Orthod Dentofacial Orthop. 2007; 132:511-7.
54. Nusstein J, Reader A, Nist R, Beck M, Meyers WJ. Anaesthetic efficacy of the supplemental intraosseous injection of 2% lidocaine with 1:100000 epinephrine in irreversible pulpitis. J Endod. 1998; 24:487-91.
55. Hargreaves KM, Keisler K. Local anesthetic failure in endodontics: mechanisms and management. Endodontic Topics. 2002; 1:26-39.
56. Noguera-Gonzalez D, Cerda-Cristerna BI, Chavarria-Bolaños D, Flores-Reyes H, Pozos-Guillen A. Efficacy of preoperative ibuprofen on the success of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a randomized clinical trial. Int Endod J. 2013; 46:1056-62.
57. Ramachandran A, Khan SI, Mohanavelu D, Kumar KS. The efficacy of pre-operative oral medication of paracetamol, ibuprofen, and aceclofenac on the success of maxillary infiltration anesthesia in patients with irreversible pulpitis: A double-blind, randomized controlled clinical trial. J Conserv Dent. 2012; 15:310-4.
58. Parirokh M, Ashouri R, Rekabi AR, Nakhaee N, Pardakhti A, Askarifard S, et al. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. J Endod. 2010; 36:1450-4.
59. Modaresi J, Dianat O, Mozayeni MA. The efficacy comparison of ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of inflamed teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 102:399-403.
60. Simpson M, Drum M, Nusstein J, Reader A, Beck M. Effect of combination of preoperative ibuprofen/acetaminophen on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis. J Endod. 2011; 37:593-7.
61. Ianiro SR, Jeansonne BG, McNeal SF, Eleazer PD. The effect of preoperative acetaminophen or a conbination of acetaminophen and ibuprofen on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. J Endod. 2007; 33:11-4.
62. Nusstein JM. Preoperative oral use of Ibuprofen or dexamethasone may improve the anesthetic efficacy of an inferior alveolar nerve block in patients diagnosed with irreversible pulpitis. J Evid Based Dent Pract. 2013; 13:102-3.
63. García Rodríguez LA, González-Pérez A. Long-term use of non-steroidal anti-inflammatory drugs and the risk of myocardial infarction in the general population. BMC Med. 2005; 3:17.
64. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to the use of nonsteroidal anti-inflammatory drugs: a metaanalysis. Ann Intern Med. 1991; 115:787-96.
65. Henry D, Lim LL, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J. 1996; 312:1563-6.
66. MacDonald TM, Morant SV, Robinson GC, Shield MJ, McGilchrist MM, Murray FE, et al. Association of upper gastrointestinal toxicity of non-steroidal anti-inflammatory drugs with continued exposure: cohort study. Br Med J. 1997; 315:1333-7.
67. Dugowson CE, Gnanashanmugam P. Nonsteroidal anti-inflammatory drugs. Phys Med Rehabil Clin N Am. 2006; 17:347-54.
68. Ong CK, Seymour RA. An evidence-based update of the use of analgesics in dentistry. Periodontol 2000. 2008; 46:143-64.
69. Buvanendran A, Lipman A. Nonsteroidal anti-inflammatory drugs and acetaminophen. In: Fishman S, Ballantyne J, Rathmell JP, Bonica JJ, editors. Bonica's Management of Pain. 4th ed. Baltimore: Williams and Wilkins; 2010. p.1158-71.
70. Singh G, Wu O, Langhorne P, Madhok R. Risk of acute myocardial infarction with nonselective non-steroidal anti-inflammatory drugs: a meta-analysis. Arthritis Res Ther. 2006; 8:R153.
71. Rahme E, Nedjar H. Risks and benefits of COX-2 inhibitors vs non-selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology (Oxford). 2007; 46:435-8.
72. Merlani G, Fox M, Oehen HP, Cathomas G, Renner EL, Fattinger K, et al. Fatal hepatotoxicity secondary to nimesulide. Eur J Clin Pharmacol. 2001; 57:321-6.
73. McCormick PA, Kennedy F, Curry M, Traynor O. COX-2 inhibitor and fulminant hepatic failure. Lancet. 1999; 353:40-1.
74. Doyle G, Furey S, Berlin R, Cooper S, Jayawardena S, Ashraf E, et al. Gastrointestinal safety and tolerance of ibuprofen at maximum over-the-counter dose. Aliment Pharmacol Ther. 1999; 13:897-906.

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Primena ibuprofena u suzbijanju postoperacionog bola u stomatologiji

Aleksandar Jakovljević[1], Emira Lazić[2], Neda Perunović[3], Nenad Nedeljković[2]

[1]Klinika za oralnu hirurgiju i implantologiju, Stomatološki fakultet, Univerzitet u Beogradu, Beograd, Srbija;
[2]Klinika za ortopediju vilica, Stomatološki fakultet, Univerzitet u Beogradu, Beograd, Srbija;
[3]Klinika za parodontologiju i oralnu medicinu, Stomatološki fakultet, Univerzitet u Beogradu, Beograd, Srbija

KRATAK SADRŽAJ

Bol koji se javi nakon hirurške intervencije je vrlo česta komplikacija u svakodnevnoj stomatološkoj praksi. U suzbijanju (lečenju) postoperacionog bola najčešće se prepisuju nesteroidni antiinflamatorni lekovi (NSAIL). Njihov analgetski efekat se zasniva, pre svega, na sprečavanju sinteze prostaglandina. Ibuprofen (derivat 2-propionske kiseline) je predstavnik velike grupe NSAIL, a otkriven je 1960. godine. Ovaj analgetik deluje na periferne nervne završetke s izrazitim protivupalnim efektom. Opsežna retrospektivna analiza randomiziranih kliničkih istraživanja u proteklih 40 godina pokazala je da je ibuprofen efikasan u suzbijanju umerenog i izraženog postoperacionog bola kod različitih indikacija. Osim efikasnosti, ibuprofen se odlikuje dobrom podnošljivošću i sigurnošću u poređenju sa drugim NSAIL. Cilj ovog rada bio je da se ukaže na najznačajnije farmakološke i terapeutske odlike, kao i neželjena dejstva ibuprofena u lečenju postoperacionog bola pri različitim indikacijama u stomatologiji.

Ključne reči: postoperacioni bol; nesteroidni antiinflamatorni lekovi; ibuprofen

UVOD

Bol je neprijatan čulni ili emocionalni osećaj koji se javlja kao reakcija na stvarno ili potencijalno oštećenje tkiva ili je opisan u okviru takvog oštećenja [1]. Poput drugih čulnih iskustava, i bol ima dve komponente. Prvu komponentu čini svesnost o postojanju bolnog stimulusa, a drugu emocionalni odgovor zasnovan na iskustvu [2]. Bol nastaje kada dođe do oslobađanja medijatora zapaljenja (bradikinin, histamin, leukotrijen i prostaglandin E2) u tkivu. Ove medijatore usled traume, zapaljenja ili alergijskih reakcija proizvode brojne ćelije imunskog sistema [3]. Akutni bol je najčešći razlog da pacijent zatraži medicinsku pomoć. Pojava bola se često povezuje sa stomatološkim lečenjem [4, 5]. Bol koji se javi posle stomatoloških intervencija jedna je od češćih komplikacija koje mogu remetiti kvalitet života pacijenata u periodu nakon izvođenja hirurškog zahvata [6].

U suzbijanju (lečenju) postoperacionog bola primenjuju se tri farmakološka pristupa: a) upotreba lekova koji sprečavaju medijatore zapaljenja da nadražuju pulpalne nociceptore; b) upotreba lekova koji sprečavaju širenje signala duž perifernih nerava; i c) upotreba lekova koji blokiraju centralne mehanizme percepcije bola i hiperalgezije [7]. Analgetici koji se danas koriste u lečenju pripadaju grupi opioidnih i neopioidnih lekova. Endogeni opioidni peptidi, alkaloidi opijuma, polusintetski i sintetski opioidi su opioidni analgetici. U neopioidne analgetike ubrajaju se acetaminofen (engl. *acetaminophen – APAP*) i nesteroidni antiinflamatorni lekovi (NSAIL) [8]. NSAIL su najčešće prepisivani analgetici u suzbijanju postoperacionog bola [9].

Analgetski efekat NSAIL se zasniva na sprečavanju sinteze prostaglandina. NSAIL sprečavaju stvaranje prostaglandina inhibicijom ciklooksigenaze (engl. *cyclooxygenase – COX*). COX je enzim koji pospešuje pretvaranje arahidonske kiseline, esencijalne masne kiseline smeštene u fosfolipidima ćelijskih membrana, u prostaglandine (PGs) i prostanoide. Postoje dva oblika enzima COX: konstitutivni (COX-1), koji se nalazi u mnogim tkivima (sluzokoža gastrointestinalnog trakta, bubrezi i trombociti), gde ima zaštitnu ulogu, i inducibilni oblik enzima (COX-2), koji se nalazi u malim količinama u organizmu, a povećava se usled zapaljenja, povrede i bola. Većina NSAIL su neselektivni i inhibiraju oba enzima, i COX-1 i COX-2, a protivupalni efekat NSAIL je uglavnom posledica inhibicije COX-2, dok inhibicijom COX-1 najčešće nastaju neželjena dejstva [8, 10].

Ibuprofen, derivat 2-propionske kiseline, otkriven je 1960. godine. Ovaj analgetik deluje na periferne nervne završetke s izraženom protivupalnom aktivnošću [11]. Pripada grupi neselektivnih inhibitora ciklooksigenaze (COX-1 i COX-2) [12]. Kao analgetik uveden je u upotrebu radi prevazilaženja komplikacija u vezi s primenom kortikosteroida u lečenju reumatoidnog artritisa, ali i drugih neželjenih dejstava tadašnjih NSAIL [13].

Cilj ovog rada bio je da se predstave farmakološke i terapijske odlike i neželjena dejstva ibuprofena u lečenju postoperacionog bola u stomatološkoj praksi.

FARMAKOLOŠKA SVOJSTVA IBUPROFENA

Ibuprofen ima hiralnu strukturu i u kliničkoj upotrebi je u obliku smese R (-) i S (+) enantiomera. Za većinu farmakoloških osobina ibuprofena odgovoran je njegov S (+) enantiomer. U istraživanjima *in vitro* pokazano je da je S (+) enantiomer 160 puta jači od R (-) oblika ibuprofena u inhibiciji stvaranja prostaglandina. Dodatno se nakon oralne upotrebe 50–60% R (-) oblika ibuprofena metabolički pretvara u S (+) oblik u intestinalnom traktu i jetri [14, 15, 16].

U rutinskoj kliničkoj upotrebi ibuprofen se najčešće unosi oralno. Pored ovakvog načina unošenja u organizam, može se primeniti i površinski, intraokularno, intravenski, intramuskularno, odnosno rektalno. Za odrasle pacijente uobičajena dnevna doza je od 1,2 do 1,8 g ibuprofena (najveća dnevna doza je 2,4 g). Za decu uobičajena dnevna doza za oralnu upotrebu je 20–40 mg/kg [17]. Kada se unosi oralnim putem, apsorpcija ibuprofena je ubrzana i potpuna. Oralna upotreba efervescentnog oblika ibuprofena odlikuje se bržom apsorpcijom i značajno većom koncentracijom u plazmi u odnosu na film-tablete (t_{max}<0,25 sata za granularni oblik i oko dva sata za film-tablete).

Poput drugih NSAIL, ibuprofen se u velikoj meri veže za proteine plazme (99%) [18]. Odlikuje se malom zapreminom

distribucije (10–15 l za osobu težine 70 kg), malim vrednostima klirensa (0,01–0,05 l/kg/min) i kratkim poluživotom leka (2,1 sat) [19]. Ibuprofen se metaboliše u jetri pomoću citohromnih enzima P450 2C9, CYP-2C8 i 2C19. Osnovni metabolički proces je konjugacija ibuprofena sa glukuronskom kiselinom, kako bi se dobili acilni glukoronidi. Izlučivanje leka i njegovih metabolita se odvija mokraćom i fecesom. Ibuprofen se mokraćom izlučuje u vidu konjugovanih metabolita, dok se deo leka izluči i u nepromenjenom obliku. Oštećena funkcija bubrega može da doprinese otežanom izlučivanju metabolita leka i njihovom nakupljanju u organizmu. Oboljenja jetre i cistična fibroza mogu da utiču na proces metabolizma ibuprofena [18-21].

KLINIČKE IMPLIKACIJE PRIMENE IBUPROFENA U RAZLIČITIM GRANAMA STOMATOLOGIJE

Opsežna analiza randomiziranih kliničkih istraživanja u proteklih 40 godina ukazala je na efikasnost ibuprofena u suzbijanju umerenog i izraženog postoperacionog bola u različitim granama stomatologije [22]. Efikasnost ibuprofena u lečenju postoperacionog bola ogleda se nakon izvođenja oralnohirurških zahvata. Upotreba NSAIL u prevenciji nastanka postoperacionog bola nakon izvođenja hirurških intervencija je često opisivana u literaturi. Veći stepen traume dovodi do razvoja zapaljenjskih reakcija u tkivu (bol, otok, crvenilo i poremećaj funkcije tkiva) i obično nastaje nakon izvođenja težih hirurških intervencija.

Hirurško vađenje impaktiranih umnjaka je jedan od češćih hirurških zahvata u svakodnevnoj stomatološkoj praksi [23]. Leken (*Lökken*) i saradnici [24] su prvi ukazali na efikasnost ibuprofena nakon obostranog vađenja umnjaka. Oni su prikazali značajnu razliku u efikasnosti ibuprofena u suzbijanju postoperacionog bola nakon obostranog vađenja umnjaka u grupi od 24 pacijenta u odnosu na placebo grupu. Ranija istraživanja su vršena zarad ispitivanja efikasnosti ibuprofena od 200, 400, 600 i 800 mg u lečenju postoperacionog bola nakon vađenja impaktiranih umnjaka [25, 26, 27]. Prikazano je da ibuprofen od 400 mg, u poređenju sa drugim dozama leka, omogućava maksimalno suzbijanje postoperacionog bola i trajanje analgetskog efekta leka [26, 27]. Takođe, u istraživanju Averbuha (*Averbuch*) i Kacpera (*Katzper*) [28] potvrđen je analgetski efekat ibuprofena od 400 mg i pokazano da nisu neophodne veće doze ovoga leka u suzbijanju postoperacionog bola.

Simor (*Seymour*) i saradnici [29, 30] su poredili brzinu nastanka i efikasnost postignute analgezije nakon vađenja impaktiranih umnjaka između efervescentnog oblika i film-tablete ibuprofena. Oba oblika ispitivanog leka bila su efikasna u suzbijanju postoperacionog bola. Rezultati istraživanja pokazuju da primena efervescentnog oblika doprinosi bržem nastanku analgezije u poređenju sa film-tabletama u prvih 30 minuta. Predstavljeni rezultati ranijih studija potvrđeni su u studiji Šarme (*Sharma*) i saradnika [31], koji su dokazali da efervescentne granule ibuprofena obezbeđuju brži nastanak analgezije nego film-tablete. Smatra se da brži nastanak analgezije usled primene efervescentnog oblika leka nastaje kao posledica brže apsorpcije, bržeg vezivanja za proteine plazme i lokalnog efekta ibuprofena [29, 30, 31].

Preventivna upotreba NSAIL, pre izvođenja hirurškog zahvata, može sprečiti centralno nadraživanje blokiranjem prenošenja nervnih impulsa do centralnog nervnog sistema. Takođe, može sprečiti periferno nadraživanje sprečavanjem oslobađanja medijatora bola u oštećenom tkivu [32, 33]. Dion (*Dionne*) i saradnici [34, 35] istraživali su analgetski efekat ibuprofena primenjenog pre i posle hirurškog vađenja impaktiranih umnjaka. Rezultati istraživanja su pokazali da je preventivna upotreba ibuprofena u dozi od 400 mg doprinela odloženom nastanku i smanjenju jačine postoperacionog bola, bez povećanja neželjenih efekata leka.

U suzbijanju postoperacionog bola nakon izvođenja hirurških zahvata dokazana je veća efikasnost ibuprofena u odnosu na aceklofenak [36] i celekoksib [37]. Takođe je dokazano da ibuprofen primenjen u kombinaciji s ketorolakom [38] i oksikodonom [39] ima veću efikasnost u lečenju postoperacionog bola nakon hirurških zahvata. S druge strane, rezultati Jošija (*Joshi*) i saradnika [40] nisu ukazali na značajnu razliku u efikasnosti ibuprofena u odnosu na diklofenak i acetaminofen s kodeinom u suzbijanju postoperacionog bola nakon hirurškog vađenja impaktiranih umnjaka.

Efikasnost NSAIL je dokazana i u lečenju postoperacionog bola nakon izvođenja parodontoloških hirurških zahvata [41, 42, 43]. Etlin (*Ettlin*) i saradnici [44] su u randomiziranom, trostruko slepom, placebo-kontrolisanom istraživanju potvrdili veću efikasnost ibuprofena u odnosu na placebo u suzbijanju bola tokom i nakon obrade parodontalnih džepova. Autori su se osvrnuli na rezultate eksperimentalnih istraživanja i kliničkih studija koji pokazuju da NSAIL učestvuju u smanjenju stope resorpcije alveolarne kosti inhibicijom medijatora zapaljenja i tako doprinose lečenju parodontalnih oboljenja [41-44]. Rezultati istraživanja ukazuju na protivupalni efekat ibuprofena i u lečenju gingivitisa usled inhibicije medijatora zapaljenja [45, 46].

Salvi (*Salvi*) i saradnici [47] su dokazali da se efikasnost NSAIL ubrzano smanjuje sa oslobađanjem leka iz organizma. Ovi autori smatraju da bi razvoj topikalnih preparata NSAIL za svakodnevnu upotrebu (poput gelova, pasti, tečnosti za ispiranje) u budućnosti mogao doprineti rešavanju ubrzanog opadanja efikasnosti ovih lekova.

Bol koji nastaje nakon ortodontskog lečenja takođe je moguće rešiti analgetskim efektima ibuprofena. Rezultati studija pokazuju da neposredno nakon postavke ortodontskih aparata koji dovode do pomeranja zuba kod pacijenta nastaje bolna neugodnost [48, 49]. Na osnovu teorije o pritisku i napetosti, medijatori zapaljenja, poput prostaglandina E_1 (PGE_1) i PGE_2, učestvuju u procesu pomeranja zuba. Posledično, PGE_1 i PGE_2 su uključeni u nastanak bola usled ortodontskog pomeranja zuba [50]. Rezultati studija o upotrebi NSAIL nakon ortodontskog pomeranja zuba su pokazali da je ibuprofen efikasan u suzbijanju bola nakon započinjanja ortodontske terapije. Takođe, dokazano je da preventivna primena ibuprofena u dozi od 400 mg oko sat vremena pre ortodontskog lečenja sprečava nastanak bola i smanjuje bolne neugodnosti kod pacijenata usled inhibicije medijatora zapaljenja [51, 52, 53].

Nemogućnost postizanja duboke anestezije kod zuba s ireverzibilnim pulpitisom je dobro poznat klinički simptom. Sprovodna anestezija, kojom se anesteziraju oralne grane donjovilič nog živca (mandibularna anestezija), najčešće je korišćena tehnika za postizanje lokalne anestezije potrebne u donjoj vilici. U 30–80% slučajeva kod pacijenata s ireverzibilnim pulpitisom mandibularna anestezija nije dovoljna za postizanje bezbolnosti tokom tretmana [54]. Osnovni razlozi ovome su brza resorpcija i smanjena disocijacija anestetičkog rastvora u kiseloj sredini,

ali i povećana ekscitabilnost nervnih završetaka u upaljenom području [55]. Rezultati istraživanja su pokazali da ibuprofen (sat vremena pre primene mandibularne anestezije u dozi od 600 mg) značajno doprinosi postizanju duboke anestezije kod pacijenata sa simptomatskim ireverzibilnim pulpitisom [56, 57, 58]. Takođe, Moderasi (*Moderasi*) i saradnici [59] su pokazali da ibuprofen u dozi od 400 mg sat vremena pre endodontskog lečenja kanala korenova zuba značajno doprinosi postizanju duboke anestezije, smanjenju bola tokom i nakon instrumentacije i povećanju komfornosti pacijenata. S druge strane, ranije objavljena istraživanja nisu potvrdila efikasnost NSAIL u postizanju veće bezbolnosti i komfora pacijenata za vreme i posle endodontskog lečenja zuba [60, 61]. U tom slučaju Nusten (*Nussten*) [62] je kao rešenje predložio dodatne infiltracione anestezije (pulpalna, intraperiodontalna) radi povećanja bezbolnosti i komfornosti pacijenta.

NEŽELJENA DEJSTVA IBUPROFENA

Upotreba NSAIL se povezuje i s nastankom određenih neželjenih dejstava. Najčešća blaga neželjena dejstva obuhvataju mučninu, povraćanje, proliv, vrtoglavicu i glavobolju, dok se teža neželjena dejstva javljaju u vidu produženog krvarenja nakon hirurških zahvata, otkazivanja bubrega, te oštećenja gastrointestinalnog i kardiovaskularnog sistema. Rizik od pojave neželjenih efekata NSAIL usled kratkotrajne upotrebe i malih doza leka je veoma mali. S druge strane, pokazano je da se usled dugotrajne primene NSAIL (duže od godinu dana) povećava rizik od oštećenja gastrointestinalnog i kardiovaskularnog sistema [63].

Oštećenje gastrointestinalnog sistema je najčešće neželjeno dejstvo NSAIL. Oštećenja nastaju kao posledica neselektivne inhibicije enzima ciklooksigenaze, posebno COX-1, koji je uključen u zaštitne mehanizme želudačne sluzokože. Svi neselektivni NSAIL su povezani s povećanim rizikom od nastanka gastrointestinalnih komplikacija u vidu krvarenja, perforacija ili opstrukcije [64]. Poređenjem pojedinih NSAIL potvrđeno je da ibuprofen ima najmanji rizik, diklofenak i naproksen umeren, a piroksikam i ketorolak najveći rizik za nastanaka gastrointestinalnih oštećenja [65, 66]. Oštećenja gastrointestinalnog trakta, usled primene NSAIL, češće se javljaju kod starijih osoba, kod pacijenata sa drugim oboljenjima gastrointestinalnog trakta i onih s pozitivnim testovima na *Helicobacter pylori*, odnosno osoba koje koriste steroidne i antikoagulantne lekove i velike doze NSAIL [67]. Radi smanjenja nastanka neželjenih dejstava u gastrointestinalnom traktu, preporučuje se poštovanje nekoliko pravila pri upotrebi NSAIL. Ukoliko je moguće, treba upotrebljavati drugu vrstu neopioidnih analgetika (selektivni, COX-2 analgetici), primeniti manje doze NSAIL u kraćem vremenskom intervalu, a kod visokorizičnih pacijenata uključiti i dodatnu terapiju za prevenciju nastanka peptičkog ulkusa – inhibitore COX-2 enzima [68].

Svi NSAIL mogu dovesti do nastanka tromba, te srčanog i moždanog udara. Tromboksan (TX_{A2}) i prostaciklin (PGI_2) su prostanoidi koji su uključeni u regulaciju vaskularnog tonusa i nastanka tromboze. TX_{A2} je vazokonstriktor koji omogućava agregaciju trombocita. S druge strane, PGI_2 je vazodilatator koji onemogućava agregaciju trombocita. Fiziološke funkcije trombocita se zasnivaju na izbalansiranom odnosu PGI_2 na endotelu krvnih sudova i TX_{A2} na trombocitima. Trombociti su veoma osetljivi na inhibiciju enzima COX, jer ne mogu da ga sintetišu. NSAIL mogu da povećaju rizik od nastanka tromba, jer dugotrajna primena velikih doza ovih lekova dovodi do smanjenja koncentracije PGI_2, dok nivo TX_{A2} ostaje nepromenjen [69]. Neselektivni NSAIL, kao i inhibitori COX-2, mogu da dovedu do nastanka tromba, srčanog i moždanog udara [70]. S druge strane, istraživanje Ramea (*Rahme*) i saradnika [71] pokazuje da primena ibuprofena dovodi do manjeg rizika za nastanak tromba i srčanog i moždanog udara u odnosu na acetaminofen, aceklofenak i celekoksib.

Ostala neželjena dejstva NSAIL, poput otkazivanja bubrega i oštećenja jetre, ređe se javljaju. Usled ekspresije enzima COX-2 u tkivu bubrega, efekat neselektivnih i COX-2 selektivnih NSAIL na funkciju bubrega, odnosno poremećaj odnosa elektrolita i nastanak perifernih edema je istovetan. U osnovi poremećaja je inhibicija stvaranja prostaglandina u bubrezima koji direktno učestvuju u autoregulaciji protoka krvi kroz bubrege. Povećan rizik od nastanka perifernih edema i hiperkalemije se javlja kod osoba sa šećernom bolesti, starijih osoba i pacijenata koji u lečenju koriste diuretike koji štede kalijum i inhibitore angiotenzin-konvertujućeg enzima (ACE-inhibitori) [69]. Nekoliko ranijih istraživanja ukazalo je na nastanaka akutnog hepatitisa i zastoja rada jetre koje je nastalo usled upotrebe COX-2 inhibitora, posebno nimesulida [72, 73]. Oštećenje jetre se, pak, retko javlja kao neželjeno dejstvo usled upotrebe ibuprofena [74]. Kontraindikacije za primenu NSAIL su: čir na sluzokoži gastrointestinalnog trakta, teška oštećenja bubrega, srca i jetre, trudnoća (poslednji trimestar) i alergijske reakcije na NSAIL [8].

ZAKLJUČAK

Terapija bola je važan aspekt stomatološke zaštite. Ibuprofen je efikasan u suzbijanju bola posle hirurškog zahvata kod širokog spektra indikacija, jer poseduje dobru efikasnost, bezbednost i podnošljivost. Racionalna upotreba leka dovodi do efikasnog lečenja postoperacionog bola uz minimalnu mogućnost nastanka neželjenih efekata leka.