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# Surgical preparation: anesthesia & hemostasis

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The intra-operative control of pain and hemorrhage represents significant factors that are required for modern, effective, and efficient endodontic surgical procedures. This review focuses on these important issues and emphasizes the level of clinical evidence of various studies reporting on interventions to alter pain or hemorrhage. To accomplish this goal, the review will provide an overview of the fundamental properties of local anesthetics and hemostasis and then build upon this foundation to provide evidence-based recommendations for treatment considerations.

## Anesthesia

Local anesthetics are widely used to provide regional analgesia for both surgical and non-surgical procedures. Although endodontic surgical procedures can be performed under general anesthesia and this regimen offers advantages for certain patient populations (such as patients who are very phobic about the treatment or those who have a mental disability), the additional cost, and increased morbidity and mortality rates compared with local anesthesia preclude its widespread use in endodontic surgery (1, 2). Local anesthetics are used to achieve three major goals in endodontic surgical procedures: (1) anesthesia during surgery; (2) hemostasis during surgery; and (3) prolonged post-surgical pain control. This latter property is due to a combined action of the drug on inhibiting peripheral neuronal discharges (min–hour duration), thereby reducing the subsequent development of central sensitization (hour–days duration).

### Mechanism of action of local anesthetics

Most local anesthetics exert their effect by diffusing across the plasma membrane and binding to the inner pore region of sodium channels. This prevents the inflow of sodium ions thus resulting in blockade of neuronal depolarization (3). As a result, the transfer of signals from the peripheral tissues to the central nervous system is blocked.

Local anesthetics differ in terms of their properties such as potency, duration of action, speed of onset, and differential neural block (Table 1). The potency of an anesthetic is inversely related to the concentration of the agent required to inhibit sodium channels (4). Any alterations that increase the lipid solubility of anesthetics such as alkalinization also increase their potency (5–8). The duration of action of an anesthetic also depends on its lipid solubility, protein binding, and rate of systemic absorption. Highly lipophilic agents such as bupivacaine, ropivacaine, and tetracaine have a long duration of action.

Several types of sodium channels have been identified in the last decade (9). An important group is the tetrodotoxin (TTX)-resistant channels. The activity of TTX-resistant channels has shown to be increased by prostaglandin E2 (PGE2), nerve growth factor, serotonin and other mediators (10–12). Because these channels are only 1/4 as sensitive to lidocaine as compared with other sodium channels, their increased activity during inflammation is thought to account, in part, for the failure of local anesthetics in inflamed tissues (Fig. 1) (11, 13). In addition, these data suggest that tissue inflammation may reduce the threshold for activation of these channels, possibly contributing to the peripheral mechanisms for reduced pain threshold

**Table 1. Selected properties of local anesthetics**

| | p$K_a$ | Speed of onset | Duration of action | Protein binding (%) |
|---|---|---|---|---|
| **Amides** | | | | |
| Lidocaine | 7.8 | Fast | 1.5–2.0 h | 64 |
| Mepivacaine | 7.8 | Slow | Up to 3 h | 77 |
| Bupivacaine | 8.1 | Slow | | 95 |
| Ropivacaine | 8.1 | Slow | Up to 6 h | 94 |
| Etidocaine | 7.9 | Fast | | 94 |
| Prilocaine | 7.9 | Fast | 2–3 h | 55 |
| Articaine | 7.8 | Fast | | 95 |
| **Esters** | | | | |
| Cocaine | | Slow | N/A | 98 |
| Procaine | | Slow | | 6 |
| 2-Chloroprocaine | 9.0 | Rapid | 45–65 min | |
| Tetracaine | | Slow | | 76 |
| Benzociane | 3.5 | Slow | N/A | |

Data taken from Clinical pharmacology of local anesthetics by John Tetazalff. Duration of action is based on data when the agent is used for infiltration.
N/A, not applicable.

(allodynia) or increased responsiveness to painful stimuli (hyperalgesia) observed in inflamed tissue such as post-surgical wounds. Based upon the key role of PGE2 in sensitizing this channel, it is possible that the non-steroidal anti-inflammatory drug (NSAID) class of drugs enhances the efficacy of local anesthetics by reducing PGE2-mediated channel phosphorylation (14).

A number of different surgical models have been used to evaluate local anesthetics. These include surgeries of the head and neck such as oral surgery (i.e. exodontia) and periodontal surgery. The oral surgery model utilizes patients undergoing surgical extraction of their impacted third molars and is generally recognized as a major test for evaluating new analgesic drugs. Other models that may be used to evaluate local anesthetics include minor surgical procedures such as bunionectomy, arthroscopic knee surgery, and tonsillectomy. Relatively few studies have evaluated anesthetics in patients undergoing surgical endodontic procedures. This review includes studies evaluating the efficacy of local anesthetics in normal volunteers as well as those conducted in patients undergoing surgery.

## Pain control during surgery

This section provides a review of the clinical trials evaluating the efficacy of various local anesthetics.

*Lidocaine*: Multiple randomized clinical trials have evaluated the efficacy of lidocaine as a local anesthetic (15–21). A randomized clinical trial evaluating the efficacy of 3.6 mL of 2% lidocaine with 1 : 100 000 epinephrine for inferior alveolar nerve block reported that although all of the subjects reported the presence of lip anesthesia, pulpal anesthesia (as determined by a lack of response to the electric pulp tester) was obtained in only 39% of central incisors, 50% of lateral incisors, and 68% of canines (15). While this study was not

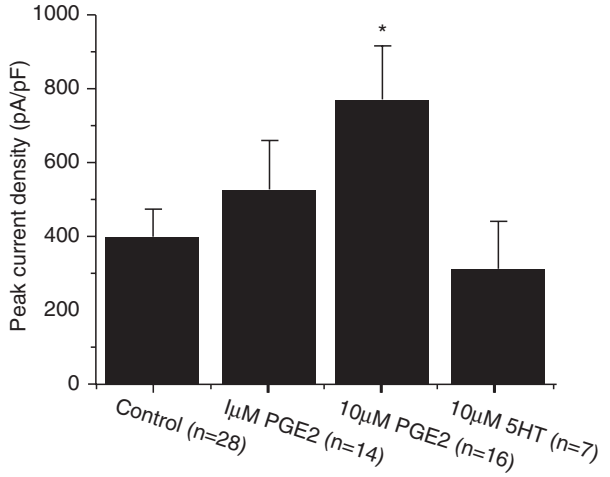


**Fig. 1. Effect of prostaglandin E2 (PGE2) or 5-hydroxytryptamine (5-HT) on peak current density in the tetrodotoxin-resistant sodium channel Nav1.9 in mouse DRG neurons. *$P<0.05$ From: Rush and Waxman (11). PGE2 increases tetrodotoxin-resistant Nav 1.9 sodium current in mouse DRG neurons via G-proteins. *Brain Res*: 2004: 1023: 264–271. Reproduced with permission from Elsevier.**

conducted in subjects undergoing endodontic surgery, it is possible to extrapolate from this and other similar studies as both soft tissue (e.g. lip anesthesia) and nociceptor (e.g. pulp anesthesia) are assessed.

The labial or lingual infiltration injection of 2% lidocaine with 1 : 100 000 epinephrine or 2% lidocaine with 1 : 50 000 epinephrine over the mandibular lateral incisors of healthy volunteers resulted in pulpal anesthesia in 43–50% of the subjects as evaluated by a randomized, double-blinded study (15). In another randomized study, 2% lidocaine with 1 : 100 000 epinephrine was administered by an inferior alveolar nerve block injection followed by a labial infiltration over the apex of the mandibular lateral incisor (16). This resulted in pulpal anesthesia in 62% of the tested lateral incisors. The administration of lidocaine for inferior alveolar nerve block resulted in pulpal anesthesia in 54–84% of the posterior teeth, as reported in a randomized clinical trial (22).

Other clinical trials have examined the effects of lidocaine with different concentrations of epinephrine. A randomized clinical study compared the effects of 3.6 mL of lidocaine with either 1 : 50 000, 1 : 80 000, or 1 : 100 000 for inferior alveolar nerve block (20). No significant differences were detected between the magnitude and duration of pulpal anesthesia obtained by the three different solutions during the 50 min post-injection period. Similar results were reported by a randomized clinical trial comparing the anesthetic efficacy of 1.8 mL of 2% lidocaine with 1 : 100 000 epinephrine, 3.6 mL of 2% lidocaine with 1 : 200 000 epinephrine, and 1.8 mL of 4% lidocaine with 1 : 100 000 epinephrine for inferior alveolar nerve block (23). This finding that the volume of lidocaine used for inferior alveolar nerve block does not result in a greater degree of success in achieving pulpal anesthesia was replicated in yet another clinical trial conducted on normal volunteers (21).

A double-blind study compared the efficacy of 2% lidocaine with 12.5 μg/mL epinephrine versus 2% lidocaine with clonidine15 μg/mL in subjects undergoing surgical removal of impacted or partially impacted lower third molars (24). The duration and intensity of anesthesia did not differ in the two groups of subjects. The onset of anesthesia as evaluated by subjects' report of lip numbness occurred earlier in the clonidine group. However, when the pin prick test was used to evaluate the onset of anesthesia, no significant difference was detected between the clonidine and epinephrine groups. This study also examined the number of patients who took ibuprofen (400 mg) during the 24 h post-operative period. While this information was not collected from a third of the subjects in the clonidine group, the available data indicated that the total number of patients who consumed analgesics in the 24 h post-operative period was significantly lower in the clonidine group as compared with the lidocaine group.

Taken together, data from these clinical trials demonstrate that lidocaine provides predictable success when used for maxillary infiltration, inferior alveolar nerve block, or for intraosseous injections. It is possible that a combination of lidocaine with clonidine results in less post-operative pain and is thus a better alternative than lidocaine with epinephrine for surgical procedures (25). However, this needs to be evaluated in prospective endodontic clinical trials.

*Articaine*: Although articaine has a reputation for providing improved local anesthetic effect, results from multiple clinical trials comparing articaine and lidocaine reveal that they are both equally effective (26–28). For example a recent randomized, double-blinded study conducted using a cross-over design and normal volunteers demonstrated that 4% articaine with 1 : 100 000 epinephrine did not differ from 2% lidocaine with 1 : 100 000 epinephrine when used to obtain inferior alveolar nerve blocks (29).

The efficacy of articaine in anesthetizing maxillary teeth was evaluated in a study in which normal volunteers were randomly assigned to receive 2% lidocaine with 1 : 100 000 epinephrine, 4% articaine with 1 : 200 000 epinephrine, and 4% articaine with 1 : 100 000 epinephrine by maxillary infiltration (30). While this study reported that the use of articaine resulted in a shorter onset and longer duration of action than lidocaine, this finding was not observed in two other similar studies (31, 32).

In conclusion, it is yet to be demonstrated that the use of articaine results in greater magnitude or duration of anesthesia as compared with lidocaine. Well-designed, randomized clinical trials are needed to evaluate and compare the effects of articaine with that of other anesthetics in endodontic surgical trials.

*Mepivacaine*: The efficacy of mepivacaine when administered for obtaining inferior alveolar nerve block was evaluated in a randomized, double-blinded, clinical study in which subjects were administered a masked cartridge of 3% mepivacaine, 4% prilocaine, or 2% lidocaine with 1 : 100 000 epinephrine (33). This study was conducted using the repeated measures design such that each subject received an inferior alveolar injection using masked cartridges of each solution at three successive appointments. No statistically significant differences were detected in the onset, success or failure, and duration of pulpal anesthesia among the three solutions. Thus, mepivacaine is a suitable anesthetic and is comparable to lidocaine.

*Bupivacaine*: The efficacy of bupivacaine when administered for inferior alveolar nerve block was evaluated in a randomized, double-blind study conducted using a cross-over design (22). The administration of lidocaine resulted in a faster onset of lip numbness while administration of bupivacaine resulted in a longer duration of lip numbness. The authors concluded that lidocaine was more effective than bupivacaine as determined by comparing the magnitude of pulpal anesthesia assessed with an electric pulp tester. While bupivacaine may not be as effective as lidocaine in achieving intra-operative anesthesia, it is very effective in reducing post-operative pain. This is discussed in detail later in this review.

*Ropivacaine*: This is the S-enantiomer of bupivacaine (34) and its efficacy was reported to be similar to that of bupivacaine in a double-blind, randomized study in normal volunteers (35). This was a double-blind repeated measures design where subjects received three maxillary anterior infiltrations at three separate appointments, consisting of 0.5% ropivacaine plain, 0.5% ropivacaine with 1 : 200 000 epinephrine, and 0.5% bupivacaine with 1 : 200 000 epinephrine. This study failed to detect any significant differences between the three solutions regarding anesthetic success and post-injection pain (Fig. 2). Administration of plain ropiva-

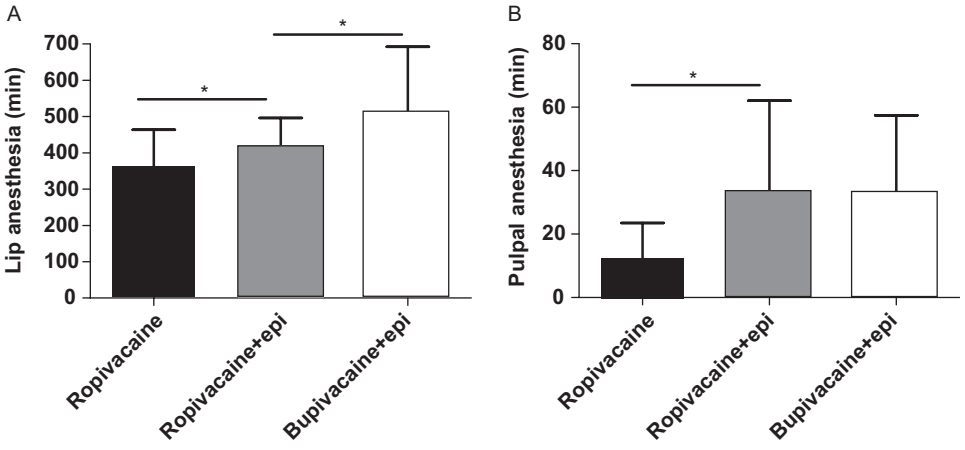


**Fig. 2. Duration of lip and pulpal anesthesia following administration of 0.5% ropivacaine plain, 0.5% ropivacaine+1 : 200 000 epinephrine, or 0.5% bupivacaine with 1 : 200 000 epinephrine. (A) Significant differences were detected between the duration of pulpal anesthesia following administration 0.5% ropivacaine plain and 0.5% ropivacaine+1 : 200 000 epinephrine and between 0.5% ropivacaine+1 : 200 000 and 0.5% bupivacaine with 1 : 200 000 epinephrine. (*$P<0.05$). (B) Significant differences were detected between 0.5% ropivacaine plain and 0.5% ropivacaine+1 : 200 000 epinephrine for pulpal anesthesia (*$P<0.05$). From: Kennedy M et al. (35). Anesthetic efficacy of ropivaccine in maxillary anterior infiltration.** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. **2001: 91: 406–412. Reproduced with permission from Elsevier.**

caine resulted in a shorter duration of pulpal anesthesia than the other treatments. No differences were detected between the duration of pulpal anesthesia with ropivacaine with epinephrine, and bupivacaine with epinephrine. However, the duration of lip anesthesia was significantly shorter following administration of 0.5% ropivacaine with 1 : 200 000 epinephrine, as compared with that of 0.5% bupivacaine with 1 : 200 000 epinephrine. Other clinical trials using much smaller sample sizes have also evaluated the effects of ropivacaine (36, 37). One of these studies failed to detect significant differences between ropivacaine and bupivacaine regarding the onset and duration of anesthesia, blood loss or post-operative pain experienced (37). Ropivacaine has the added benefit of having a lower potential for cardiovascular toxic effects (38, 39). The cardiotoxicity potency ratios for levobupivacaine, racemic bupivacaine, and ropivacaine, based on lethal dose is: 2.1 : 1.2 : 1, based on an animal study (39). Thus, ropivacaine has the advantage of being the least cardiotoxic among the currently available long-acting anesthetics.

*Levobupivacaine*: Like ropivacine, this is another S( − ) enantiomer of bupivacaine. The difference between the two is the length of the N-substituent, which is a butyl group for levobupivacaine and a propyl group for ropivacaine (40). Using the oral surgery model, a randomized, double-blind, clinical trial evaluating bupivacaine and levobupivacaine demonstrated that the two agents did not differ regarding the onset and duration of action and post-operative pain experienced (41). A randomized, double-blind, placebo-controlled clinical trial of subjects undergoing extraction of their impacted third molars demonstrated that administration of 0.75% levobupivacaine prior to surgery resulted in lower pain ratings and a longer time to request rescue medication than the administration of 2% lidocaine with 1 : 80 000 epinephrine (42). Another randomized double-blind study demonstrated that pre-incisional infiltration with levobupivacaine results in less post-operative pain as compared with ropivacaine (43). Thus, levobupivacaine is suitable for the control of post-surgical pain.

Multiple studies have evaluated the effects of warming the anesthetic solution on reducing the pain of injection. These randomized clinical trials were evaluated in normal volunteers, or patients undergoing dental procedures or minor surgical procedure such as eyelid surgery. While some of these studies have reported that warming the anesthetic to body temperature reduces injection pain as compared with anesthetic administered at room temperature (44–50), others have failed to detect any effect on injection pain (49, 51). *In vitro* studies have demonstrated that cooling lidocaine increases the duration of its effect, but this is yet to be evaluated clinically (8).

Buffering lidocaine with sodium bicarbonate is also reputed to reduce the pain experienced during injection. The results of many (52–54), but not all (55, 56), of these randomized clinical trials have reported that buffering of anesthetic solution results in significant reduction in pain during injection.

Hyaluronidase has been used as an adjunct to aid the onset of local anesthesia. It is an enzyme that cleaves hyaluronic acid, and thus is thought to facilitate the diffusion of the local anesthetic through the extracellular matrix. A randomized, double-blind study was conducted to determine the anesthetic efficacy of a buffered lidocaine with epinephrine solution compared with a combination of buffered lidocaine with epinephrine plus hyaluronidase solution in inferior alveolar nerve blocks (57). No differences were noted in the anesthetic effect of both the solutions. However, the combination lidocaine/hyaluronidase solution resulted in a significant increase in post-operative pain and trismus. Thus, it appears that the use of hyaluronidase should be avoided.

## Pain control in the postoperative period

Although local anesthetics are primarily used to reduce pain during surgery, they also play a role in post-operative pain control. This is achieved by two mechanisms. First, local anesthetics provide immediate (min–hrs) pain control via blockade of discharges from peripheral nerves. Second, the prolonged blockade of peripheral input acts to attenuate the component of post-operative pain that is due to central sensitization. Central sensitization refers to the amplification in responsiveness that occurs in the central nervous system in response to prolonged nociceptor stimulation (58, 59). Central sensitization is thought to mediate, at least in part, the central component of hyperalgesia and allodynia and is therefore an important mechanism for post-operative inflammatory pain conditions. The prolonged exposure to input from nociceptors (especially the unmyelinated C fiber nociceptors) results in allodynia and hyperalgesia. A key feature of central

sensitization is that it is due to a prolonged discharge of peripheral nociceptive neurons, in particular, the unmeylinated C fibers (60, 61). This property has an important clinical implication because it suggests that long-acting local anesthetics might produce profound post-operative analgesia even days after a single injection of the drug. The results from double-blind randomized clinical trials in post-surgical dental pain patients provide experimental support for this hypothesis. A randomized clinical trial conducted by Gordon et al. (62) elegantly demonstrated that administration of 0.5% bupivicaine immediately after extraction of impacted third molars resulted in decreased pain at later time periods (Fig. 3). In a subsequent study, minimizing the peripheral nociceptive barrage during the immediate post-operative period resulted in significantly less post-operative pain as compared with blocking the barrage during surgery. Thus, the prolonged nociceptor input from the first few hours *after* surgery appears to be a clinically significant factor in developing central sensitization. This finding supports the clinical recommendation that long-acting local anesthetics (e.g. bupivacaine) be injected at the completion of surgical procedures which may significantly reduce post-surgical pain for prolonged periods of time.

Similar results have been reported using other surgical models such as periodontal surgery and tonsillectomy (63–65). Although future randomized clinical trials using endodontic surgical patients are required, it is possible that the use of long-acting anesthetics such as bupivacaine in endodontic surgery will attenuate the development of central sensitization, resulting in decreased pain following endodontic surgical procedures.

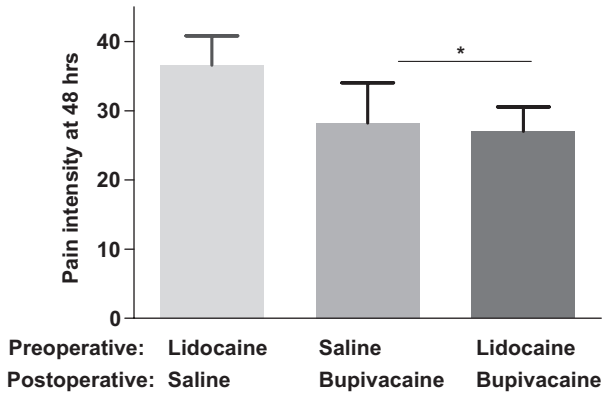


**Fig. 3. Pain intensity reported on a 100 mm visual analog scale 48 h after extraction of impacted third molars. Subjects in this study received either 2% lidocaine pre-operatively, 0.5% bupivacaine post-operatively, both, or placebo *$P<0.05$. Data from: Gordon SM et al. (62). Attenuation of pain in a randomized trial by supression of peripheral nociceptive activity in the immediate postoperative period.** *Anest. Analg* **2002: 95(5):1351–1357. Reproduced with permission from Lippincott Williams & Wilkins.**

An important question to be addressed here is whether the administration of the anesthetic before or after surgery affects the attenuation of post-operative pain (66). A non-randomized clinical trial evaluated the effect of administration of 0.5% plain bupivacaine before and after extraction of impacted third molars. Subjects in this study had all their impacted third molars extracted at a single appointment under general anesthesia. The impacted third molars were extracted on one side 10 min after administration of bupivacaine. On the contralateral side, bupivacaine was administered after the molars were extracted. Pain intensity ratings from both sides were collected for up to 6 days after surgery. No significant differences were detected between the two sides. This study provides additional support to the conclusion that the nociceptive barrage induced by surgical manipulation (e.g. incision, tissue reflection, osteotomy, etc) is not as important as the post-operative barrage induced by tissue inflammation for the development of central sensitization.

A recent meta-analysis has evaluated whether NSAIDs, local anesthetics, systemic opioids, *N*-methyl D-aspartate (NMDA) antagonists, or epidural analgesics provide significant pre-emptive analgesia in post-surgical pain patients. This meta-analysis consisted of 66 randomized-controlled trials totalling 3261 patients and compared the same analgesic administered either in the pre-operative or post-operative periods (67). All the studies in this meta-analysis were randomized and double-blinded, and were published between January 1987 and October 2003. The exclusion criteria were studies in which pre-operative administration of the analgesic was compared with placebo or no treatment, comparison of different pre-operative and post-operative drug treatments, and comparison of pre-operative administration with a combination of pre-operative and post-operative administration. The primary outcome measures analyzed were pain intensity scores, consumption of supplemental analgesics, and time to first rescue analgesic. The mean difference in the outcome variables between the pre-operative and post-operative groups for each study was converted into an 'effect size'

and then an overall mean across all studies was calculated. An effect size of 0 indicates no difference between pre-operative and post-operative drug administration, a positive value indicates that pre-emptive analgesia is effective and a negative effect size indicates that pre-emptive analgesia is ineffective. The results of this meta-analysis indicate that pre-operative administration of NSAIDs improved time to first rescue analgesic request (effect size +0.68, $P<10^{-8}$) and reduced analgesic consumption (effect size +0.48, $P = 0.00000003$) (Fig. 4). However the post-operative pain scores were not significantly reduced (effect size +0.14, $P = 0.09$). The latter is likely because of the fact that the reduction in pain intensity is so great that differences between pre-operative and post-operative administration of NSAIDs could not be elucidated (the so-called 'floor effect'). When all three outcome measures were combined, the effect size for NSAIDs was +0.39 and the combined *P*-value was $<10^{-8}$, which is a highly significant difference favoring pre-emptive administration. Similarly, pre-operative local anesthetics had significant beneficial effects for reducing the need for supplemental analgesics and increased the time before the first analgesic was requested. In contrast, NMDA antagonists and systemic opioids were less robust in their effects.

A series of three randomized, cross-over studies using the oral surgery model evaluated the effect of pre-

| | Number of studies | Total number of subjects | P value |
|---|---|---|---|
| **Pain Scores** | | | |
| NSAIDs | 12 | 617 | .09 |
| Local anesthetics | 11 | 535 | .26 |
| Systemic Opioids | 7 | 324 | .04 |
| NMDA antagonists | 7 | 418 | .97 |
| Epidural analgesia | 13 | 653 | .00 |
| **Supplemental analgesics** | | | |
| NSAIDs | 12 | 582 | .00 |
| Local anesthetics | 8 | 360 | .00 |
| Systemic Opioids | 4 | 194 | .12 |
| NMDA antagonists | 7 | 418 | .09 |
| Epidural analgesia | 13 | 640 | .00 |
| **Time to first analgesic** | | | |
| NSAIDs | 6 | 307 | .00 |
| Local anesthetics | 7 | 306 | .00 |
| Systemic Opioids | 2 | 74 | .16 |
| NMDA antagonists | 4 | 258 | .34 |
| Epidural analgesia | 9 | 368 | .00 |

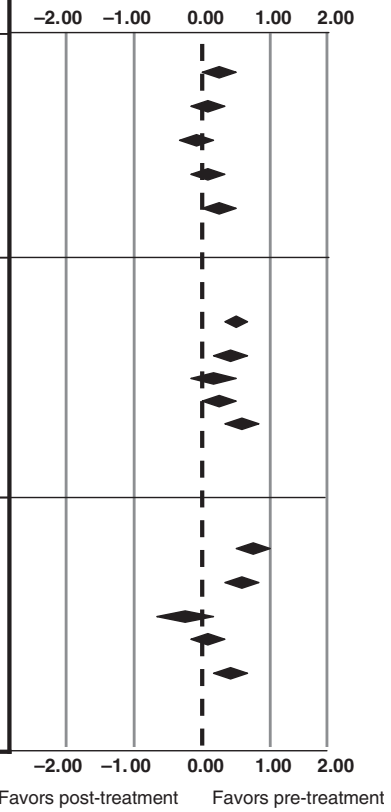


**Fig. 4. Results from a meta-analysis comparing the effects of various drugs for preemptive analgesia. Studies included in this analysis randomly administered the same drugs either pre-operatively or post-operatively and measured pain (visual analog scale), the need for supplemental ('rescue') analgesics, and the time before the first post-operative analgesic was requested. The results are displayed using a Forrest plot, also known as an odds ratio plot, which graphs the mean odds ratio (with 95% confidence intervals) calculated from two to 13 clinical studies. The table displays the number of studies, sample size, and *P* value for each outcome measure. The diamond in the plot displays the effect size obtained by pooling all the trials for each analgesic regimen. An effect size of 0 indicates no effect, a positive effect size indicates that pre-emptive analgesia is effective, and a negative effect size indicates that pre-emptive analgesia is ineffective. Data from: Ong CK et al. (67). The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* 2005: 100 (3): 757–773. Reproduced with permission from Lippincott Williams & Wilkins.**

operative and post-operative administration of flurbiprofen as compared with acetaminophen in combination with oxycodone (68). The local anesthetics used in this study were either etidocaine or lidocaine. Factorial comparison of their data demonstrated that flurbiprofen suppresses post-operative pain independent of the local anesthetic used. Based on these as well other clinical trials, the pre-emptive use of NSAIDs is an effective method of reducing post-surgical pain.

Some studies have evaluated the use of topical anesthetics in the management of post-operative pain. A placebo-controlled, randomized, double-blind study on children who underwent tooth extractions demonstrated that the application of swabs soaked with 0.25% bupivacaine with 1 : 200 000 epinephrine after surgery for 5–10 min resulted in less post-operative pain than placebo (69).

## Adverse effects

Local anesthetics have been associated with both regional and systemic side-effects. Regional complications include paresthesia, hematoma formation and bleeding. Local nerve damage may be due to improper needle placement. A 21-year retrospective study on the incidence of paresthesia following administration of local anesthetics revealed a greater incidence of paresthesia associated with the administration of both articaine and prilocaine than predicted based upon usage (70). This study only includes non-surgical cases and thus ruled out surgical trauma as the causative factor for paresthesia. The study also evaluated the type of needles used, and the available data do not support any relationship between needle type and incidence of paresthesia.

Systemic effects of local anesthetics involve both the cardiovascular system and the central nervous system. A retrospective study documenting the incidence of morbidity and mortality in the practices of members of the Massachusetts Society of Oral and Maxillofacial Surgeons reported that in patients who were given local anesthetics alone the most common adverse event was syncope which occurred in one out of every 160 patients (71). Other adverse events included acute angina pectoris (1/29 775 patients), hypotension (1/35 729 patients), hypertension (1/44 662 patients), dysrhythmia (1/89 324 patients), and convulsions (1/10 509 patients).

A number of clinical trials have examined the hemodynamic effects of local anesthetics. The hemodynamic effects induced by maxillary infiltration of 3.6 mL of lidocaine with 1 : 80 000 epinephrine with those induced by ergometer exercise were compared in a clinical trial (72). The workload of the ergometer stress test was comparable to that of walking for 4.8 miles or doing light yard work. Echocardiography was performed to assess the hemodynamic changes induced. This study demonstrated that the hemodynamic effects induced by administration of the local anesthetic were less than those induced by the ergometer stress test.

Using a prospective randomized study with a crossover design, Wood et al. (73) examined the venous blood levels of lidocaine and change in heart rate after intraosseous and infiltration injections of 1.8 mL of 2% lidocaine with 1 : 100 000 epinephrine. The results of this study demonstrated that intraosseous administration of 2% lidocaine with 1 : 100 000 epinephrine (adrenalin) resulted in a transient tachycardia ($\sim$ 9 beats per minute, b.p.m.) that was greater than peak levels observed after maxillary infiltration even though the plasma lidocaine levels were similar following both routes of administration. Similar results were reported by a study examining changes in blood pressure in healthy volunteers who were administered a mandibular intraosseous injection of 2% lidocaine with 1 : 100 000 epinephrine (74). The administration of the anesthetic solution caused a transient elevation in heart rate but no change in systolic and diastolic blood pressure.

A randomized, double-blinded clinical trial compared the effect of intraosseous infiltration of 2% lidocaine with 1 : 100 000 epinephrine with those of 3% mepivacaine (75). No differences in blood pressure were reported between subjects receiving the two anesthetics. Intraosseous administration of mepivacaine had no effect on heart rate while administration of lidocaine with epinephrine resulted in an increase of heart rate in 67% of the subjects. A double-blind study examining the effect of 4% articaine with 1 : 200 000 epinephrine, 3% plain mepivacaine, and 3% prilocaine with felypressin 1 : 1 850 000 demonstrated that no significant hemodynamic changes occurred with respect to the basal values when administered in healthy patients subjected to surgical removal of a lower third molar (76). Multiple other studies of different local anesthetic agents in normal volunteers have reported similar results (77–79).

A double-blinded clinical study compared the effects of 2% lidocaine with clonidine or epinephrine in

subjects undergoing extraction of their mandibular third molars (24). No significant differences were detected in the systolic blood pressure, diastolic blood pressure and mean arterial pressure between groups. Heart rate was significantly increased in the epinephrine group 5 min after administration of anesthesia and during surgery compared with the clonidine group and with basal values. While the studies mentioned above were conducted in normal volunteers, others have examined the effect of local anesthetics with epinephrine in patients with significant cardiac problems. A double-blinded study examined the effect of local anesthetics in cardiac transplant patients with those in subjects without any cardiovascular disorders (80). The cardiac patients, who were more than 3 months post-transplant, received 2% lidocaine with 1 : 80 000 epinephrine or 3% prilocaine with 0.03 IU/mL felypressin as maxillary buccal and palatal infiltration anesthesia. The healthy volunteers were administered 2% lidocaine with 1 : 80 000 epinephrine. The change in systolic and diastolic blood pressure following administration of anesthetic as compared with their baseline values did not differ among the three groups. Tachycardia was noted in the cardiac transplant patients who received the epinephrine containing anesthetic. The mean increase in heart rate as compared with baseline was $23 \pm 7.1$ b.p.m. This sustained increase in heart rate was not observed in the other two experimental groups. The mean increase in transplant patients who received prilocaine was $-0.2 \pm 6.8$ b.p.m. and $4.8 \pm 7.9$ b.p.m. in the healthy patients who received epinephrine containing anesthetic.

From the above studies, it can be concluded that local anesthetics can be safely administered to subjects with certain cardiovascular problems and that it may be prudent to restrict the amount of epinephrine administered to about 4.4 mL of a 1 : 80 000 solution (80).

Methemoglobinemia is a rare complication of prilocaine and articaine (81–84). Risk factors include anemia and cardiopulmonary disorder. The early symptoms of methemoglobinemia are headache, lethargy, tachycardia, weakness, cyanosis, and dizziness. As the condition worsens, dyspnea, acidosis, cardiac dysrhythmias, heart failure, seizures, and coma may occur (85). Methemoglobinemia is not detected by pulse oximeters and may give a misleading impression of patient oxygenation (86). It is spontaneously reversible and may be treated by intravenous administration of methylene blue.

The toxic effects of local anesthetic on the central nervous system (CNS) include excitation followed by depression. CNS toxicity may first cause some symptoms such as lightheadedness, dizziness, and visual and auditory disturbances including tinnitus (87). These are followed by signs of CNS excitation such as muscular tremors of the face and extremities and generalized tonic–clonic convulsions. These symptoms may then be followed by CNS depression resulting in drowsiness, unconsciousness, coma, respiratory depression, and arrest. In certain cases, the CNS depression may occur very rapidly without the preceding excitation. These include cases where the drug administration has been very rapid, such as in intravascular injections, or in patients who are under the effect of CNS depressants.

*Prevention and management of systemic toxicity*: The systemic toxicity of local anesthetics can be prevented by avoiding the use of excessive doses and by using aspiration to detect the intravascular location of the needle. The management of toxic effect includes the use of oxygen when the early signs of toxicity are first detected. Anticonvulsants (such as intravenous benzodiazepines or barbiturates) must be administered if the patient has a systemic seizure. Cardiovascular toxicity, especially owing to bupivacaine, can be resistant to therapy and may require the use of large doses of ionotropic drugs.

## Future directions

Recent advances include the use of peripherally acting opioid antagonists. A number of animal studies have demonstrated that the local administration of opioids has an analgesic effect when administered into inflamed tissues. These effects are not seen when the opioids are applied to normal tissues and instead, the rapid development of competence of the peripheral opioid receptors is triggered by the release of inflammatory mediators such as bradykinin (88). The presence of peripheral opiate analgesia in humans was demonstrated in a series of double-blind, placebo-controlled, clinical trials (89). These trials were conducted using the endodontic model of hyperalgesia and the oral surgery model in order to evaluate both chronic and acute inflammation. In the first part of the study equal volumes of sterile saline placebo, local anesthetic (2% mepivacaine with 1 : 20 000 levonordefrin), or morphine sulfate (0.4, 1.2, or 3.6 mg) were injected into

the intraligamentary space in subjects with a diagnosis of pulpal necrosis and acute exacerbation of a chronic apical periodontitis. Using both a 100 mm visual analog scale and a 4-point category scale, a time-related analgesic effect of morphine was detected, which peaked at the 15–20 min time interval. When the effects of systemically (subcutaneous administration into the volar forearm) and locally (intraligamentary) administered morphine sulfate (1.2 mg) were compared using the same model, it was seen that local administration of morphine had a significant analgesic effect, while the effect of systemically administered morphine did not differ from placebo. A randomized clinical trial found that the administration of articaine plus 1 mg morphine into inflamed resulted in significant and prolonged analgesia in the post-operative period following tooth extraction as compared with injection of the same solution into normal tissue (90).

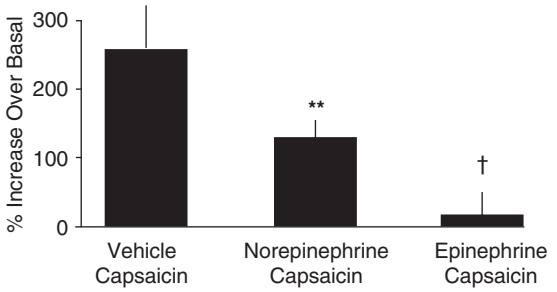


**Fig. 5. Effect of pre-treatment with vehicle, norepinephrine (10 nM), or epinephrine (10 nM) capsaicin-evoked release of immunoreactive calcitonin gene-related peptide from *in vitro*-superfused dental pulp. **$P<0.01$ vs. vehicle. †$P<0.01$ vs. vehicle and norepinephrine. Reproduced with permission from Bowles et al. (94).**

Another randomized clinical trial compared the effects of subcutaneous administration of tramadol (2 mg/kg) with that of 1 mg/kg lidocaine (1 mg/kg) in subjects undergoing minor surgery (lipoma excision and scar revision) (91). In subjects who received tramadol, the time for first analgesic use was longer and the total number of analgesics consumed in the 24 h post-operative period was lower than in those who received lidocaine.

Yet another effective strategy to reduce peri- and post-operative pain is by using adrenergics. Small-diameter sensory neurons are known to express both α- and β-adrenergic receptors (92, 93). A recent study on bovine dental pulp demonstrated that adrenergic agonists such as epinephrine and clonidine inhibit capsaicin-evoked neuropeptide release (Fig. 5) (94). Capsaicin is known to selectively activate a ligand-gated ion channel known as TRPV1, which is expressed on a major class of nociceptors. The use of adrenergics in high concentrations for better hemostasis during surgery offers an additional advantage of preventing nociceptor activation. Thus, adrenergics may be used in the future as peripheral analgesics, possibly combined with local anesthetics.

Anecdotal evidence suggests that red heads require more local anesthetic than others to achieve profound analgesia. A recent study by Liem et al. (95) compared the effect of 1% lidocaine in red-haired and dark-haired women. Subjects in this study were exposed to noxious electrical stimulation after subcutaneous injections of 1% lidocaine. The results indicated that red-haired women were more resistant to the anesthetic effects of subcutaneous lidocaine than dark-haired women,

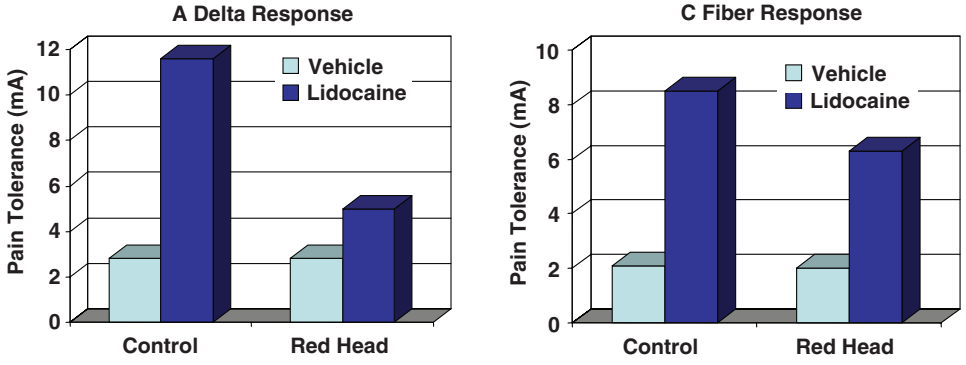


**Fig. 6. Pain tolerance threshold in women with red or dark hair ($n = 60$). Electrical stimuli were applied on the forearms of subjects 5 min after administration of 2 mL of 1% lidocaine. Controls had uninjected areas on the same forearms. Subcutaneous lidocaine was less effective in women with red hair as compared with women with dark hair, $P = 0.005$. Data from: Liem EB et al. (95). Increased sensitivity to thermal pain and reduced subcutaneous lidocaine efficacy in redheads. *Anesthesiology* 2005: 102(3): 509–514. Reproduced with permission from Lippincott Williamson & Wilkins.**

particularly when evaluating stimuli sufficient to activate A-delta nociceptors (Fig. 6). More studies are required to replicate these findings in endodontic pain patients and to elucidate whether red-heads simply require higher dosages of lidocaine to obtain adequate anesthesia.

## Mechanisms of hemostasis

Well-controlled hemostasis is a critical factor for surgical procedures and the post-operative course of healing (96, 97). In one study of 60 patients undergoing endodontic surgery, the amount of intra-operative hemorrhage ranged from 1 to 48 mL, with the duration of surgery being a major predictor of bleeding (98). Although this comparatively small magnitude of bleeding implies that endodontic surgical procedures are generally well tolerated in healthy patients, case reports indicate that patients with coagulopathies may have substantial blood loss during comparatively atraumatic endodontic procedures (99). In addition to the potential medical risk, the delivery of modern endodontic surgical procedures requires superb visualization of the surgical field. Thus, knowledge of the mechanisms and management of hemostasis is an essential skill for endodontic surgery.

A simplified overview of mechanisms of hemostasis (Fig. 7) provides a foundation for assessing the pre-operative patient and managing hemostasis in the intra- and post-operative periods. The induction of vascular injury triggers four major phases of hemostasis (100–103).

The first phase of hemostasis involves vasoconstriction at the site of injury and is elicited by the release of serotonin and thromboxane A2 (TXA2). The immediate vasoconstrictive period reduces blood flow through the injured tissue and provides some initial protection to loss of circulating volume in the vascular compartment. The vasoconstrictive phase may last up to several hours after trauma.

The second component of hemostasis involves platelet adhesion and degranulation. Activated thrombin promotes the adherence of platelets to exposed collagen fibers, leading to the development of a soft plug of platelets. The 'clumping' of platelets is promoted by activated fibrinogen. Two classes of hemostatic agents, collagen and adrenergic agonists (e.g. epinephrine), promote activation of platelets and this contributes to their mechanism of action (103).

The third phase of hemostasis involves clot formation that occurs due to the release of factors from platelets and injured tissue that trigger the clotting cascade and the development of a fibrin/platelet plug at the site of injury (100–103). Activated platelets release ADP, TXA2, serotonin, Factor V, and other substances such as phospholipids and lipoproteins. The formation of fibrin polymers entraps platelets and erythrocytes, leading to a stable plug formation. Although it should be recognized that both the intrinsic and extrinsic pathways mediate clot formation (Fig. 8), more recent studies emphasize the rapid temporal integration of both pathways in clinical settings (100, 102, 103), rather than a simplistic division into either intrinsic or

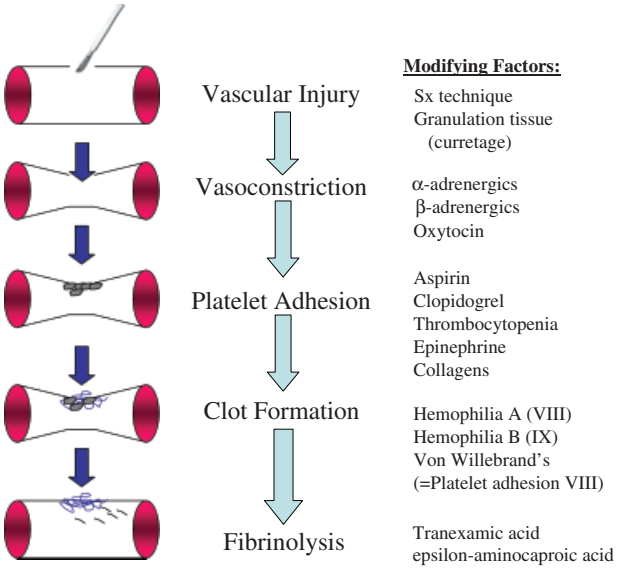


**Fig. 7. Schematic illustration of the hemostatic pathways illustrating the impact of selected drugs or disorders on hemostasis.**

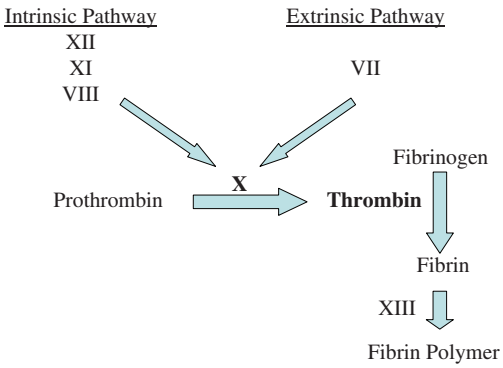


**Fig. 8. Intrinsic and extrinsic pathways of the clotting cascade.**

extrinsic pathways of clotting. It should be readily appreciated that enzymatic activation of multiple levels of downstream enzymes is a highly efficient mechanism for amplification. In general, the intrinsic pathway occurs when blood contacts the negative charges of proteins embedded in the basement membrane of connective tissues or RNA released from injured cells (100). The intrinsic pathway involves factors XII (Hageman factor), XI, VIII, prekallikrein, and high-molecular-weight kininogen; this pathway is so named because all of these factors are 'intrinsic' to the vascular compartment. In contrast, the extrinsic pathway, occurs extremely rapidly, augments the activity of the intrinsic pathway and is activated by tissue injury. The extrinsic pathway involves factor III (tissue factor) and factor VII; this pathway is 'extrinsic' as it involves a tissue factor (factor III) found outside of the vascular compartment. From a surgical perspective, the extrinsic pathway is critically important, and indeed, the tissue factor-induced initiation of this pathway is thought to contribute to most clinical situations involving the coagulation pathway (103). The two pathways merge with the activation of factor X leading to the common coagulation pathway (100). The mechanical product of this cascade, fibrin, forms the structural elements of the clot. However, it should be appreciated that the enzymes activated in this pathway contribute to other functions (e.g. chemotaxis, etc), resulting in a coordinated response to tissue injury.

Finally, the fibrinolytic pathway mediates the dissolution of the fibrin/platelet plug in the post-operative period (Fig. 7). The enzyme plasmin is responsible for fibrinolysis and two forms of the inactive precursor circulate in blood. Plasmin rapidly cuts fibrin at a minimum of 50 amino-acid sites, leading to efficient depolymerization (104). Dental surgical procedures impact fibrinolysis activity in saliva, and in turn, oral hemostasis is altered by acquired (e.g. tranexamic acid, epsilon-aminocaproic acid) or developmental abnormalities of the fibrinolytic system (105).

## Pre-operative assessment

Although a certain level of intra-operative bleeding is expected with surgical trauma, the clinician should suspect an acquired or inherited bleeding disorder when bleeding is evident from many sites even after initial good hemostasis. Although this may be easily correctable in certain cases (i.e. curettage of granulation tissue), it emphasizes the need for appropriate pre-operative assessment. In contrast, consistent bleeding from a single site is usually associated with surgical trauma to a larger vessel or a highly vascular structure (e.g. sinus) (100). Given the complexity of the clotting cascade, it is not surprising that many diseases and drugs can alter hemostasis (Table 2). Accordingly, the pre-operative evaluation of the patient's medical history represents a critical time for assessing the presence and magnitude of a risk for altered hemostasis and for planning modifications to the surgical plan (106, 107).

Several diseases are well recognized to interfere with the clotting cascade, leading to poor hemostasis. von Willebrand's disease is the most common heritable bleeding disorder and the three major subtypes of this disease are due to a deficiency of Factor VIII levels or activity. A case series of 63 patients with von Willebrand's disease undergoing dental extractions concluded that local treatment with tranexamic acid and fibrin glue with desmopressin (0.3 μg/kg) minimizes bleeding problems in the majority of cases (108). Other case series provide similar conclusions (109). In one series of three female patients with von Willebrand's disease, the pre-operative treatment with estrogen (as either oral contraceptives or HRT) was reported to reduce surgical bleeding as compared with their prior experiences (110). In one case series of 16 patients with Hemophilia A or B undergoing extractions, the combined use of local treatments (e.g. fibrin glue, gelatin packing, and post-operative application of tranexamic acid) and systemic treatments (e.g. dihydro-D-arginine vasopressin) produced good hemostasis in the majority of cases. Hemophilia B (Factor IX deficiency) comprises about 15% of all hemophilia cases and case reports describe the successful management of nine hemophilia B patients for dental surgery by combined administration of antifibrinolytc agents (e.g. ε-aminocaproic acid or tranexamic acid) with monoclonal antibody purified factor IX (MAb factor IX) (111). Recombinant-activated factor VII (rFVIIa, NovoSeven™; Novo Nordisk, Princeton, NJ, USA) has been used to promote hemostasis in patients with hemophilia A or B, liver disease, thrombocytopenia, or thrombocytopathia and has been characterized as a 'universal' hemostatic agent because of its ability to activate thrombin directly (112–115). Moderate-to-severe factor XI deficiency because of several genetic

**Table 2. Common disorders of hemostasis**

| Class | Example |
|---|---|
| Hypocoagulability | |
| Impaired platelet function | Drugs (e.g., aspirin) |
| | Radiation |
| | Splenomegaly |
| | Autoimmune |
| Impaired clotting activity | Impaired protein synthesis (e.g., vitamin K) |
| | Classic hemophilia (Factor VIII; ~ 80% of all hemophilias) |
| | Hemophilia B (Factor IX; ~ 15% of all hemophilias) |
| | Hemophilia C (Factor XI; ~ 5% of all hemophilias) |
| Hypercoagulability | |
| Increased platelet function | Atherosclerosis |
| | Diabetes |
| | Smoking |
| Increased clotting activity | Pregnancy |
| | Oral contraceptives |
| | DIC (disseminated intravascular coagulation) |

Table adapted from: http://www.pathoplus.com/blood.htm.

polymorphisms has been reported in Ashkenazi Jews and is associated with risks in hemostasis during dental surgical procedures (116, 117). Platelet disorders can be categorized by a lack of sufficient concentration of platelets (thrombocytopenia) or lack of adequate function (thrombasthenia), and case reports are available describing dental surgical procedures for both conditions (118, 119).

Other diseases or conditions promote the clotting cascade leading to extensive clot formation. Examples include disseminated intravascular coagulation (DIC), antithrombin III deficiency, Protein C deficiency, protein S deficiency, and oral contraceptive use. Type II diabetics have reduced fibrinolytic activity, and these patients may present for treatment with fibrinolytic agents (120).

Many drugs are well recognized to alter hemostasis. For example, patients often take oral anticoagulant therapy for several indications including reduction of risk for stroke or myocardial infarction (121, 122). In one randomized study, patients were administered aspirin (100 mg/day) and either continued aspirin to the day of tooth extractions or stopped taking aspirin 7 days before surgery. Although the continuous aspirin-treated patients had significantly greater values as evaluated by standard laboratory bleeding tests, both groups were in the normal range for bleeding time (1–3 min), and there was no clinical difference in the amount of surgical bleeding (123). The authors concluded that local hemostatic control was sufficient for surgical treatment of patients on low-dose aspirin and that drug cessation was not indicated. However, in one case report of a patient with immunosuppressants secondary to organ transplant, treatment with a low-dose aspirin therapy was associated with substantial intraoral hemorrhage following a dental surgical procedure; a platelet transfusion was required for hemostasis (124). Patients take warfarin as anticoagulant therapy for many indications. A randomized clinical trial on 109 patients (international normalized ratio (INR) $<4.1$) indicated that cessation of warfarin for 2 days prior to the procedure had no effects on clinically important post-operative bleeding after extractions as compared with patients who continued warfarin therapy (125). A randomized-controlled trial evaluated 31 patients taking coumarin for changes in INR after acetaminophen treatment (1500 or 3000 mg/day $\times$ 14 days); the use of this analgesic did not produce clinically significant changes in INR values (126). Antibiotics have been reported to interfere with vitamin K metabolism (presumably by interference with gastrointestinal bacterial populations) in certain patients (127), and a case report has attributed post-operative bleeding to amoxicillin-induced vitamin K deficiency in a patient treated with oral irrigation with a tranexamic acid (4.8%) mouth rinse (128).

The pre-operative assessment should include questions specifically pertaining to the use of herbal or alternative medications. Systematic reviews of the literature indicate that problems related to hemostasis (e.g. garlic, ginkgo, and ginseng), cardiac rhythmicity

(e.g. ephedra), or drug interactions (e.g. ginseng, kava, St John's wort, and valerian) can occur with many commonly used herbal medicines (129, 130). A case report suggests that chronic abuse of cocaine may be associated with post-extraction hemorrhage (131), possibly due to alterations in adrenergic receptor activity.

Pre-operative assessment should include collection of a thorough medical history and possible consideration of laboratory testing to provide an objective measure of some component of the clotting cascade. The relative value of these tests and recommended clinical management have been discussed in recent reviews (100, 103, 132). The partial thromboplastin time test (PTT) assesses the intrinsic coagulation system and uses a negatively charged surface to activate this pathway. The prothrombin time (PT) evaluates the critical extrinsic coagulation pathway and assesses for deficiencies in fibrinogen and Factors II, V, VII, and X. The INR provides a standardized value for the PT test and is often used to assess the coagulation status of patients with congenital or acquired coagulation disorders. Patients on anticoagulation therapy have been recommended to have INR values of 1.5–2.5 prior to dental surgery as a compromise between minimizing the potential for thrombosis while attempting to attain reasonable hemostasis (133). More recently, several clinical studies, case series, and reviews have recommended maintenance of oral anticoagulation therapy, in an attempt to avoid thrombotic events, and have instead focused on local hemostatic interventions to maintain hemostasis in dental surgical procedures (123, 125, 134–140). For example, in one prospective, randomized-controlled clinical trial, 250 patients on oral anticoagulant therapy were compared with 250 control patients, and the incidence of post-operative bleeding after tooth extraction was compared. The oral anticoagulant group had local hemostatic treatment (e.g. fibrin sponge, silk sutures, and post-operative compression with a gauze saturated with tranexamic acid) and there was no difference in the incidence of post-operative bleeding complications (1.6% vs. 1.2%, respectively) between the two groups (141). An extensive discussion of these risk : benefit issues of this approach is available (100, 142, 143), and medical consultation may be indicated in these situations (144). In addition, the INR does not appear to predict post-operative bleeding. In one case series of 249 patients undergoing 543 extractions, patients with INR values of 1.00–1.99 (5% bleeding), 2.00–2.49 (12.8% bleeding), 2.50–2.99 (15.2% bleeding), 3.00–3.49 (16.6% bleeding), and INR > 3.50 (13% bleeding) all had similar incidences of bleeding (134). The authors concluded that local surgical treatment (gelatin sponge and sutures) without cessation of anticoagulant therapy was sufficient for hemostasis, and that INR levels within these ranges do not appear predictive for post-operative bleeding. Similar results have been reported for 66 patients with abnormal laboratory test values associated with factor XII deficiency, dysfibrinogenemia, the lupus-like anticoagulant, and pseudothrombocytopenia (145); in general, local treatment conditions are sufficient for surgical hemostasis in many cases. Normal platelet counts range from 150 000 to 400 000/μL, and a platelet count of at least 50 000/μL is preferred in many surgical procedures (100, 118). Interestingly, cutaneous bleeding time does not correlate with post-operative bleeding, although the duration of the surgical procedure and the presence of immediate post-operative oral bleeding time after surgery do correlate with post-operative bleeding (146).

One extensive review has recently concluded that one of the best predictors for poor surgical hemostasis is the collection of a thorough medical history that discloses a prior history of bleeding occurrences (100). Specific questions should focus on gathering information about: (1) prior history of bruising, frequency of bruising (e.g. 'Do you easily bruise?), size of bruises, etc; (2) prior history of surgeries (including tooth extractions such as third molars) and any post-operative bleeding; (3) drug use (e.g. aspirin, etc); (4) transfusions; and (5) relevant medical history (e.g. anemia, malignancies, connective tissue diseases, immune status) (147).

## Pharmacological management of hemostasis

The experienced surgeon controls hemostasis using a variety of both pharmacological and non-pharmacological methods. Although these topics are divided in this review for purposes of logical presentation, it should be appreciated that both approaches are generally used simultaneously to achieve the desired control of the surgical field.

Adrenergic agonists ('vasoconstrictors') are widely used to promote surgical hemostasis. Clearly infiltration injection of even one 1.8 mL cartridge of 2%

lidocaine with 1 : 100 000 epinephrine produces about a threefold elevation in blood levels of epinephrine, although there are little to no detectable systemic cardiovascular effects at this dose, and the local hemostasis is of course much greater than that observed with injection of plain lidocaine (148). A randomized, double-blind, controlled clinical trial reported that hemostasis was judged to be significantly better in dental surgeries with 1 : 100 000 epinephrine containing local anesthetics as compared with 1 : 200 000 containing local anesthetics (149). Moreover, the use of lidocaine containing 1 : 50 000 epinephrine produced more than a 50% improvement in hemostasis as compared with 2% lidocaine containing 1 : 100 000 epinephrine in patients undergoing periodontal surgery (150). Thus, the use of a local anesthetic containing 1 : 50 000 epinephrine has been advocated for local infiltration around the surgical field. Clinical trials indicate that injection of local anesthetics containing 1 : 50 000 produces a transient tachycardia that returns to normal within 4 min of injection (151). In addition, it has been suggested that a slow rate of injection (e.g. 1–2 mL/min) provides time for lateral diffusion of the drug across the surgical field, leading to improved constriction of vessels throughout the surgical area.

Epinephrine is also available in a racemic solution for local placement into the surgical crypt. It has been recommended that packing the surgical crypt with several epinephrine-impregnated cotton pellets, applying pressure for 2–3 min, and then removing all except the first pellet will lead to effective hemostasis (152). This process can be repeated if necessary. A recent randomized-controlled clinical trial compared 33 patients undergoing endodontic surgery with local hemostasis consisting of either racemic epinephrine-containing cotton pellets (Racellet™ #3, Pascal Co. Inc., Bellevue, WA, USA) or installation of a ferric sulfate solution (Vicostat™, Ultradent Inc., South Jordan, UT, USA). Adequate hemostasis was judged to occur in 100% (17 of 17) in the epinephrine pellet group and in 94% (15 of 16) of the ferric sulfate group (153). There was no change in systemic blood pressure or pulse with either treatment group. Of course, care must be taken when removing the last cotton pellet to avoid a potential foreign body reaction due to cotton fibers left in the surgical crypt. The use of a resorbable material containing epinephrine has the potential advantage of avoiding this issue. This was addressed in a recent randomized-controlled clinical trial comparing 48 patients undergoing endodontic surgery with local hemostasis consisting of a resorbable collagen sponge (Colla-Cote™, Integra Lifesciences Corp., Plainsboro, NJ, USA) treated with either saline or with epinephrine (10 drops of 2.25% racemic epinephrine from a 0.5 mL vial; Nephron Pharmaceutical Corp, Orlando, FL, USA). The Colla-Cote sponge (1 × 2 cm) was impregnated with saline or epinephrine, packed into the surgical crypt and then additional pads were added, pressure was maintained for 3–4 min, and then all except the first pad was removed. The intra-operative hemostasis was judged to be effective in 17% (1 of 6) of the saline-treated sponges and in 93% (39 of 42) of the epinephrine-treated sponges (154). There were no detectable systemic cardiovascular events as measured by blood pressure or pulse rate.

Tranexamic acid acts to inhibit fibrinolysis and thereby maintains clot integrity. In one randomized study, 49 patients on warfarin were maintained on the anticoagulant therapy and were given oral irrigation with tranexamic acid (10 mL of 4.8% solution as an oral rinse four times per day × 7 days) or an intra-operative fibrin sealant for dental extractions with local application of oxidized cellulose mesh and sutures. Both groups had similar and successful management of hemostasis, with the tranexamic acid irrigation being more cost effective (155). These findings have been replicated in other placebo-controlled randomized clinical trials (156). In another randomized study, 85 patients on warfarin were maintained on the anticoagulant therapy and were given either a 2-day or a 5-day presurgical regimen of oral irrigation with tranexamic acid (10 mL of 4.8% solution as oral rinse four times per day × 7 days) for dental extractions with local application of oxidized cellulose mesh and sutures. Both groups had similar and successful management of hemostasis, suggesting that the 2-day pretreatment with tranexamic acid irrigation was more cost effective (135). Other case reports have described systemic treatment with tranexamic acid to lead to post-operative hemostasis in patients with congenital coagulopathies undergoing dental surgery (157).

Desmopressin (1-desamino-8-D-arginine vasopressin; DDAVP; Ferring Pharmaceuticals, Sufferin, NY, USA) is a synthetic analog of vasopressin that increases Factor VIII levels. Case reports and case series indicate that DDAVP and local treatment (e.g. fibrin glue, gelatin packings, and tranexamic acid) promote hemostasis in many patients with von Willebrand's disease

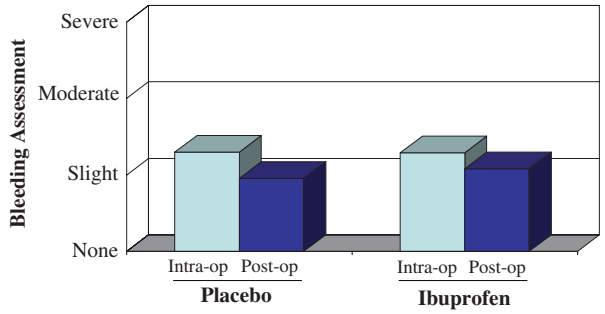


**Fig. 9. Effect of ibuprofen (400 mg tid starting 24 h before surgery and continuing for 4 days post-operatively) vs. placebo on assessment of clinical bleeding after extraction of impacted third molars. Reproduced from: Lokken P et al. (164). Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: a test with ibuprofen. *Eur J Clin Pharmacol* 1975: 4(8): 209–216. With kind permission of Springer Science and Business Media.**

or Factor XI deficiency undergoing surgical procedures (109, 158–161).

Thrombin is available in a power form (e.g. Thrombin-JMI; Jones Pharma Inc. St Louis, MO, USA) and, as expected, promotes hemostasis upon local administration into the surgical wound. Case series and reviews report the production of good hemostasis with local application of thrombin powder on dental surgical wounds in patients with oral anticoagulant therapy (133, 162).

Many NSAIDs are recommended for post-operative pain control. As NSAIDs (including aspirin) might influence post-operative bleeding via inhibition of cyclooxygenase, it is reasonable to consider whether NSAIDs alter post-operative hemorrhage. Although data for endodontic surgical procedures are not available, a systematic review of the effect of NSAIDs on post-operative bleeding after tonsillectomy concluded that non-aspirin NSAIDs have no significant effects on clinical bleeding, whereas aspirin does significantly increase post-operative bleeding (163). Figure 9 illustrates the effects of ibuprofen 400 mg vs. placebo on intra- and post-operative bleeding in patients undergoing extraction of impacted third molars (164).

## Non-pharmacological management of hemostasis

Surgical techniques can be considered as an integrated collection of methods and instruments designed to minimize intra-operative bleeding. The judicious design of flaps, placement of instruments, and handling of tissues provide several benefits including improved access, visibility, hemostasis, pain control, and healing (97, 152, 165–167). Although the harmonic scalpel has not yet been reported in endodontic surgical clinical trials, a randomized study on 28 patients undergoing tonsillectomy reported an 80% reduction in intra-operative bleeding after harmonic scalpel removal of one tonsil as compared with conventional scalpel dissection tonsillectomy with electrocautery on the contralateral side (168). A similar benefit for reduced bleeding was observed on comparing the harmonic scalpel with conventional procedures in 60 patients undergoing thyroidectomy (169), and reviews of this device are available in the oral surgery literature (170).

Several forms of absorbable sponges have been advocated for hemostasis. Collagen-based materials are highly purified forms of animal collagen that are available in various preparations including CollaCote™ (Integra Life Sciences Corp.), CollaStat™ (American Medical Products Inc, Freehole, NJ, USA), Instat™ (Ethicon, Piscataway, NJ, USA), and Hemocollagene™ (Septodent Inc., Kent, UK). Although these materials can be difficult to manipulate in a wet surgical field, they appear effective for promoting hemostasis without a significant delay in healing. In one study of 53 patients undergoing tumor resection, manual pressure combined with the application of a collagen sponge was compared with a novel collagen-based composite material (CoStasis™, Orthovita, Malvern, PA, USA), with a reported 70% and 100% control of hemorrhage, respectively (171). Another example of absorbable sponges is based on oxidation of alpha collagen fibers and includes Surgicel™ (Johnson & Johnson Inc., Piscataway, NJ, USA). In a case series of 26 patients on oral anticoagulants (INR = 2.1–4), the use Surgicel™ in the extraction socket was no different from fibrin glue (Beriplast P™, Centeon LTD, West Sussex, UK) for post-operative hemorrhage control (172). Studies have demonstrated slow absorption of Surgicel™ over a 120-day observation period and thus this material might have an impact on healing. A third example of absorbable sponges is based on gelatin proteins and includes Gelfoam™ (Pharmacia, Peapack, NJ, USA). Although Gelfoam™ promotes platelet activation, it has been reported to produce delayed healing.

Medical-grade calcium sulfate is used as a resorbable matrix for healing and can be placed into a surgical crypt and then carved to improve hemostasis and

visibility (152). In one randomized clinical study on 6-month healing of three-wall periodontal pockets, there was no significant difference in healing of lesions treated with calcium sulfate plus autogenous bone vs. bioresorbable membranes plus autogenous bone (173). However, a randomized-controlled study on 20 patients undergoing endodontic surgery demonstrated significantly greater healing at 1 year in the calcium sulfate (Surgiplaster™, Class Implant, Rome, Italy)-treated group (seven of 10 patients) as compared with the control group (three of nine patients) (174). These authors also reported that application of calcium sulfate tended to improve hemostasis.

Ferric sulfate (e.g. Cut-Trol™, Ichthys Inc, Mobile, AL, USA; Vicostat™, Ultradent Inc.) is a low pH (0.8–1.6) necrotizing agent that produces a chemical coagulation similar to an electrical cautery (175). The application of ferric sulfate to a bleeding surgical crypt leads to rapid hemostasis. However, the continued presence of the agent and the coagulum delays post-operative healing in animal studies (176). This emphasizes the need for curettage and irrigation at the completion of surgery, and this removal technique has been shown to result in normal healing in ferric sulfate-treated animals (175). As described previously, a recent randomized-controlled clinical trial compared patients undergoing endodontic surgery with local hemostasis consisting of either ferric sulfate treatment or placement of racemic epinephrine-containing pellets (Racellet™ #3, Pascal Co. Inc.). Both treatments produced equivalent intra-operative hemostasis (153).

Electocautery is a traditional means of producing hemostasis via coagulation and vesicular clumping (174, 177). A randomized study on tonsillectomy patients compared post-operative hemostasis where electrocautery was performed in one tonsillar crypt vs. electrocautery plus argon beam coagulation in the contralateral crypt. The results indicated that 81% of elecrocautery surgical fields and 92% of argon beam surgical sites had complete post-operative hemostasis (178). One concern raised with electrocautery techniques is the delayed bone healing that is known to occur after local production of high temperatures.

Bone wax is a mixture of purified beeswax and isopropyl palmitate. Although this is a traditionally used hemostatic agent, a concern has been raised that residual bone wax may interfere with postsurgical healing (179), and it has been demonstrated that residual bone wax allows persistent bacterial colonization in the surgical field (180). Therefore, it is not generally recommended for surgical hemostasis (96). To address this concern, a case report described the addition of calcium alginate fibers (Coalgen™, Brothier, France) to bone wax (bone wax, Ethicon, Sommerville, NJ, USA) prior to placement in an endodontic surgical crypt. This mixture led to good hemostasis and improved removal of the material (181).

An important non-surgical method of maximizing hemostasis is the removal of granulation tissue. Chronically inflamed tissue has a high density of blood vessels and is a potential source for intra-operative bleeding at the periradiacular area (98). Curettage of granulomas reduces this source of bleeding.

Lasers have been advocated for many dental indications including hemostatic control (182–184). However, in one randomized clinical trial on 50 dental implant sites, the Erbium : yttrium aluminum garnet (YAG) (Er : YAG) laser was not found to differ from conventional second-stage surgical exposure of implants for the control of hemorrhage (185).

The local application of autologous platelets or platelet-rich plasma has been reported to promote hemostasis and post-operative healing (186, 187). A recent case report using platelet-rich plasma for endodontic surgery has been described (188). However, no randomized clinical trials in endodontic surgical patients have been reported. A Cochrane Systematic Review on platelet-rich plasma for surgical hemostasis concluded that evidence supported a beneficial effect of this treatment, although many of the cited studies had a small sample size or were uncontrolled designs (189). Similarly, a Cochrane Systematic Review on fibrin sealants concluded that they were effective in promoting hemostasis, with, again, concern raised about underpowered or poorly designed studies (190).

The post-operative application of local pressure and good tissue approximation serve as common non-pharmacological techniques for the maintenance of hemostasis (191). In one randomized control study, patients on warfarin treatment underwent multiple tooth extractions in which local treatment consisted of placing gelatin sponges in the extraction sites with closure by interrupted resorbable sutures with or without external application of the adhesive *n*-butyl-2-cyanoacrylate (Histoacryl™; B. Braun, Melsungen, Germany; Glustitch™; Glustitch Inc, Delta, BC, Canada). The results indicate that the group having

adhesive tissue approximation experienced significantly less bleeding without resorting to changes in warfarin treatment (136). A case series of 130 patients undergoing root end surgery, extractions, and periodontal surgery reported that application of *n*-butyl-2-cyanoacrylate improved hemostasis and pain control (192). A second adhesive, octyl-2-cyanoacrylate, has been approved by the Food and Drug Administration for closure of incisions and lacerations, and has been shown to reduce bleeding form cutaneous lacerations (193).

## Summary

The generation of effective intra-operative anesthesia and hemostasis are critical pillars supporting the foundation of effective endodontic surgical procedures. While the use of anesthetics in endodontic surgery has not been examined extensively, we have extrapolated from other studies and it appears that anesthetics can be safely used to reduce both peri- and post-operative pain. Anesthetics including lidocaine and articaine can be used to obtain effective anesthesia of the soft and hard tissues. Post-operative pain can be effectively reduced for up to 48 h after surgery by the administration of long-acting anesthetics.

The control of hemostasis begins with the pre-operative assessment of the patient's medical history and current medication usage. Effective intra-operative hemostasis often requires the slow infiltration injection of one to two cartridges of local anesthetic containing 2% lidocaine with 1 : 50 000 epinephrine and waiting for tissue blanching as a sign of effective vasoconstriction. Excellent surgical skills including careful design of flaps, handling of tissues, positioning of retractors, etc, to reduce trauma to the tissue. Hemostasis in the surgical crypt can be managed by any of several techniques, including resorbable sponges containing epinephrine or direct application of ferric sulfate. Although additional clinical trials comparing various methods are indicated, treatment with epinephrine appears to have minimal systemic effects and avoids the potential delayed wound healing that might occur if not all of the ferric sulfate is removed. A reasonable alternative, particularly for patients at cardiovascular risk, might be the local application of a calcium sulfate paste on the surgical crypt. Good tissue approximation with appropriate suturing techniques combined with 5–10 min of wound compression is effective for promoting post-operative hemostasis in otherwise healthy patients.

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