The Correlation between Blood Pressure and Postoperative Pain in Endodontic Patients

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ABSTRACT

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The Correlation between Blood Pressure and Postoperative Pain in Endodontic Patients
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Previous studies indicate that hypertension is correlated with diminished sensitivity to experimental pain. This prospective observational study was designed to test the hypothesis that resting arterial blood pressure is inversely correlated to decreased postoperative pain following endodontic therapy. Written informed consent was obtained from patients seeking treatment for their teeth diagnosed with pulpal necrosis and periradicular periodontitis. Preoperative blood pressure was recorded and subjects rated their pre-operative pain intensity using a 100mm visual analog scale. A standardized non-surgical root canal therapy was initiated. Subjects were given a pain diary in which they recorded their post-operative pain and analgesic intake over 7 days. After controlling for pre-operative pain, a significant correlation was noted between Day 1 postoperative pain and preoperative systolic blood pressure ($p<.03$) and preoperative pulse pressure ($p<.005$). This study provides support for a functional interaction between the cardiovascular and pain regulatory systems.

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LIST OF ABBREVIATIONS

VAS	Visual Analogue Scale

INTRODUCTION

Effective pain control in both pre- and postoperative phases is an important aspect of endodontic therapy. Pain incidence in the immediate post-operative period (ie.1-7 days) ranges from 8% to 62% (*Seltzer and Bender 1961; Fox et al 1970; Mulhern et al 1982, Georgopoulou et al 1986; Sathorn et al 2008).* The incidence of persistent post-operative several months (12 -59 months) after completion of nonsurgical root canal therapy has been reported to be as high as 12% (*Polycarpou et al 2005*). While some of the factors which affect pain resolution after endodontic therapy have been identified, it is yet to be demonstrated whether preoperative arterial blood pressure affects the resolution of postoperative pain.

Numerous studies have suggested that an increased arterial blood pressure is associated with a decrease in pain perception *(Zamir and Segal 1979; Zamir, Simantov and Segal 1980; Naranjo and Fuentes 1985; Zamir and Shuber 1980; Ghione et al 1988; Sheps et al 1992).* Specifically, hypertensive rats have demonstrated less sensitivity to thermal and mechanical stimuli as compared to normotensive rats (*Zamir and Segal 1979; Naranjo and Fuentes 1985).* Clinical studies have also demonstrated this hypertension hypoalgesia phenomenon to experimental pain (*Zamir and Shuber 1980; Ghione et al 1988; Sheps et al 1992*). In a study evaluating resting systolic blood pressure and pain perception in 64 females experiencing temporomandibular disorder and 23 pain free females, it was observed that pain free high resting blood pressure subjects had

higher thermal pain tolerances and higher ischemic pain thresholds when compared to the pain-free low blood pressure subjects (*Maixner et al 1997*).

The exact mechanism for the contribution of arterial blood pressure to experimental pain sensitivity remains unknown. The hypertensive hypoalgesia effect has been shown to be reversed by the administration of the opioid antagonist naloxone suggesting that endogenous opioids may play a role between blood pressure and pain perception (*Sheps et al 1992*; *Maixner et al 1982*). However, most support for the opioid mechanism is based on animal models. In contrast, human studies have not provided such strong support for this mechanism (*Bruehl and Chung 2004*). Both preclinical and clinical studies give strong support to the role of baroreceptors in hypertensive hypoalgesia. Electrical, pharmacological, as well as physiological stimulation of baroreceptors produces diminished acute pain sensitivity (*Maixner et al 1982; Randich and Maixner 1984; D'Antono et al 2000*).

Hypertension hypoalgesia is not exclusive to experimental pain as evidenced by data collected in the Nord-Trondelag Health Survey (*Hunt 1 and Hunt 2.)* Data from these surveys reported that individuals with high blood pressure have a lower prevalence of chronic musculoskeletal complaints as compared to those with normal blood pressure (*Hagen et al 2004*). More recently Tronvik et al (*2008*) reported that increased arterial blood pressure was associated with a decreased prevalence of migraine and nonmigrainous headaches. However, these studies have not addressed odontogenic pain.

Recently at the University of North Carolina a study was conducted investigating the genetic basis of endodontic pain perception. Subjects in this study were patients undergoing initiation or completion of nonsurgical root canal therapy. Although this

study was not designed to evaluate the relationship between arterial blood pressure and pain, preliminary data suggested a significant association between diastolic arterial blood pressure and mean Day 1 postoperative pain ($p = 0.024$) (*Applebaum 2009*).

Based on the preclinical and clinical evidence supporting hypertension hypoalgesia we conducted a prospective observational study to evaluate the relationship between resting arterial blood pressure and postoperative pain associated with endodontic treatment. We hypothesized that resting arterial blood pressure is inversely correlated to decreased postoperative pain in endodontic patients. We found a significant inverse correlation between preoperative systolic blood pressure and postoperative pain Day 1 ($p=0.03$). Additionally we found an inverse correlation between preoperative pulse pressure and postoperative day 1 pain ($p=0.005$). Our results provide further evidence that there is a functional interaction between cardiovascular and pain regulatory systems. Increasing our understanding of how the human body naturally modulates and regulates pain will enhance our ability to prevent and manage pain associated with endodontic therapy.

REVIEW OF LITERATURE

A. Correlation between Blood Pressure and Pain

Preclinical and clinical studies have suggested that a correlation exists between blood pressure and pain perception. For example in a study renal hypertension was first induced by applying a clip on the left renal artery and then a modified hot plate method was used to measure analgesia (*Zamir and Segal 1979*). It was observed that hypertensive rats were less sensitive to thermal pain as compared to normotensive rats. This has also been demonstrated in a study in which hypertension was induced by short-term isolation (*Naranjo and Fuentes 1985*). Results from these 2 studies demonstrate that hypertensive rats have higher mechanical and thermal pain thresholds as compared normotensive rats.

Clinically, a relationship between blood pressure and pain thresholds was evaluated by measuring the responsiveness to electrical tooth pulp stimulation in 55 male subjects that were either normotensive or unmedicated essential hypertensive (*Zamir and Shuber 1980*). The results showed that hypertensive subjects exhibited higher pain thresholds than the normotensive subjects. In a similar study, an electric pulp tester was used to test pain thresholds in subjects with borderline or established hypertension as compared to normotensive subjects (*Ghione et al, 1988*). Sensory thresholds were significantly higher in subjects with borderline or established hypertension as compared to the normotensive groups. Furthermore, in another study a higher mean arterial blood pressure proved to be significantly related to thermal pain threshold as well as thermal

pain tolerance (*Sheps 1992*). A similar correlation between resting blood pressure and pain has been reported in women (*Maixner et al 1997*). The relationship between resting systolic blood pressure and pain perception in 64 females diagnosed with temporomandibular disorder was compared to 23 age-matched pain free female subjects. It was observed that the pain-free higher resting blood pressure subgroup had higher thermal pain tolerances, higher ischemic pain thresholds, and provided lower magnitude estimates of the intensity of graded heat pulses when compared to the pain-free low blood pressure subgroup.

Hypertension hypoalgesia is also observed in studies involving clinical pain as evidenced by data collected in two consecutive public health studies in Nord-Trondelag, Norway (*Hagen et al 2004).* The surveys were conducted between January 5, 1984, and February 15, 1986 (*HUNT 1*) and from August 1995 to June 1997 (*HUNT 2*) compromising 46, 901 adults participating in both studies. It was reported that individuals with high blood pressure have a lower prevalence of chronic musculoskeletal pain as compared to those with normal blood pressures. Furthermore, using the same HUNT 1 and HUNT 2 prospective and cross-sectional data it has been reported that increased arterial blood pressure was associated with a decreased prevalence of migraine and nonmigrainous headaches (*Tronvik et al 2008*). In a review of the HUNT study data with regards to hypertension associated hypoalgesia and reported that headache and chronic musculoskeletal complaints in all parts of the body were comorbid, and the prevalence of pain in all locations was inversely related to blood pressure levels (*Stovner and Hagen 2009*).

A clinical study of 159 male subjects undergoing radical prostatectomy evaluated preoperative blood pressure and 24h and 48h postsurgical pain intensity. The results demonstrated that post surgical pain was decreased for those men with higher presurgical systolic blood pressure (*France and Katz 1999*). There is only one study to date that has provided data related to a hypertension hypoalgesia and post operative pain associated with endodontic treatment. This was a recent study at the University of North Carolina at Chapel Hill which evaluated the genetic basis of endodontic pain perception. Subjects in this study were patients undergoing initiation or completion of nonsurgical root canal therapy. Although this study was not designed to evaluate the relationship between arterial blood pressure and pain, the preliminary data suggested a statistically significant association between diastolic arterial blood pressure and mean pain on the first post-operative day (*Applebaum 2009*).

B. Putative Mechanisms for Hypertension Hypoalgesia

Organizational Schemes:

Cannon's thalamic theory of emotions states that regions within the hypothalamus coordinate autonomic and behavioral responses to sensory stimuli by modulating the output of several central nervous system loci located caudal to the hypothalamus. Furthermore, direct thalamic-spinal projections may coordinate autonomic output and sensory input by directly modulating neural activity at the spinal level (*Cannon 1927; Maixner 1991*).

In addition to and not exclusive from Cannon's theory is the visceral theory of emotional responses by James-Lange (*Cannon 1927*). This model states

that sensory appreciation and autonomic responses to environmental stimuli are influenced by afferent input from visceral structures. In this model, the activation of visceral afferents, such as baroreceptors afferents, modulates the autonomic output and sensory-motor integration by stimulation of cell groups in the neuraxis that project to the spinal cord, which coordinate the sensory input and autonomic output (*Maixner 1991*).

Baroreceptor Activation:

Baroreceptors are pressure sensitive cells that relay information regarding blood pressure from various parts of the body to the central nervous system. They serve to help maintain a homeostasis of blood pressure during blood pressure altering events such as movement, postural change, blood loss, or psychological stress. They are also involved in regular cyclic changes as in respiration or thermoregulatory processes (*D'Antono et al, 2000).* Afferent fibers from the carotid sinus baroreceptors join their respective glossopharyngeal nerve and project to the nucleus tractus solitarii in the dorsal medulla. In turn they project efferent cardiovascular neurons in the medulla and spinal cord. In addition there are cardiopulmonary receptors that transmit their afferent signals through the vagus nerve to the same brainstem nuclei. The efferent limbs of the baroreflex loop consist of parasympathetic and sympathetic fibers to the heart, peripheral blood vessel smooth muscle, and other organs (*Kougias et al 2010*). Increase in mean arterial blood pressure leads to stimulation of the baroreceptors causing reduction of the sympathetic outflow to the peripheral vessels and the heart.

Additionally, baroreceptor activation may play a role in the regulation of nociception (*Maixner 1991*).

It has been suggested that baroreceptor activation reduces reactivity to noxious stimulation in rats (*Dworkin et al 1979, Maixner and Randich 1984*). In an experimental study Sprague-Dawley rats (N=16) were first trained to escape an aversive stimulus (an electric stimulus) by running on the top of a tread wheel. Hypertension was induced in some of the rats by infusion of phenylephrine. To test the hypothesis that baroreceptors play a role in hypertension hypoalgesia, 6 of the rats underwent surgical denervation of the carotid and aortic arch. When blood pressure was raised, the 10 rats with intact baroreceptors showed less running to avoid the noxious stimulus. The 5 successfully denervated rats did not demonstrate this behavioral response which indicates hypertension-induced baroreceptor activity reduced escape-avoidance running.

Activation of the cardiopulmonary reflex arc by volume expansion with Ficoll has shown to result in antinociception of the tail flick response to radiant heat in Sprague-Dawley rats (*Maixner and Randich 1984*). Resection of the right vagal nerve which innervates the sinoatrial node of the heart resulted in significant attenuation of antinociception. This suggests that physiologic activation of baroreceptors of the cardiopulmonary reflex results in antinociception.

In a prospective observational cohort study, 66 healthy men with a variety of risk factors for hypertension were tested by painful mechanical finger pressure that was presented three times. Significantly lower pain was reported by men with

relatively elevated systolic blood pressure following leg elevation suggesting that blood pressure related hypoalgesia may be related to cardiopulmonary baroreceptor stimulation (*D'Antono et al 2000).* Similar results were seen using Phase Related External Suction whereby external baroreceptors are stimulated by pressure or suction utilizing a neck cuff system (*Rau et al 1994*).

Endogenous Opioid Mechanisms

A relationship for blood pressure and pain sensitivity that is affected by endogenous opioids has been shown in a variety of experimental animal studies. In order to test for hypertension hypoalgesia, renal hypertension was first induced by applying a solid silver clip on the left renal artery (Zamir and Segal 1979). Following the induction of hypertension, pain threshold was measured using a modified hot plate method every 5 days during a 40 day period. Hypertensive rats demonstrated an increased pain threshold compared to the normotensive group. Following the observance of hypertension hypoalgesia, the opioid antagonist naloxone was administered to test the possibility that central opioid receptors were involved with changes in pain sensitivity. Naloxone was shown to reverse the hypoalgesia behavior in the renal hypertensive rats. In another study, the opioid antagonist naloxone was observed to eliminate the decreased sensitivity to painful stimuli in genetically hypertensive rats (*Saavedra in 1980*). Measurements of opiate activity by radiorecptor assay in several brain regions of both experimentally hypertensive rats and controls rats showed that the hypertensive rates demonstrated a 45% higher level of opioid activity in the spinal cord

compared to the normotensive rats (*Zamir Simantov and Segal 1980*). Additionally, they found that genetically hypertensive rats had higher levels of opioid activity in the spinal cord, hypothalamus and pituitary gland. Hypertension induced by short-term isolation has also been evaluated in other preclinical studies (*Naranjo and Fuentes 1985*). After establishing experimental hypertension, nociception was measured with the tail flick and paw pinch techniques. Experimentally hypertensive animals demonstrated a higher mechanical and thermal pain threshold as compared to normotensive animals. It was also observed that administration of the opiate antagonist, naloxone, reversed the hypoalgesia to experimental stimuli and also reduced systolic blood pressure. It should be noted that the finding of naloxone reducing systolic blood pressure was not observed in other studies and it is more commonly reported that naloxone reverses the hypoalgesia but does not alter arterial pressure or heart rate in either spontaneously hypertensive or normotensive rats (*Maixner et al in 1982*; *Zamir Simantov and Segal 1980*).

In clinical studies plasma beta-endorphin levels have been measured in both hypertensive and normotensive subjects. Out of groups of 10 hypertensive males and 10 normotensive males the mean arterial blood pressure was significantly related to both thermal pain threshold and thermal pain tolerance. In addition, baseline plasma levels of plasma beta-endorphin were significantly higher for the hypertensive group (*Sheps et al 1992*). A similar study using an electronic pulp tester demonstrated that hypertensive subjects with normal pulps

had higher beta-endorphin plasma levels as well as having decreased pain sensitivity (*Guasti et al 1996*).

Vagus Afferent Stimulation

Antinociception associated with stimulation of vagal afferents has been demonstrated in numerous animal studies. Denervation of the right vagal nerve trunk in genetically hypertensive rats has been shown to cause a reduction in their hypoalgesic behavior responses to aversive thermal stimuli as compared to a sham operated control group (*Maixner et al 1982*). In that same study it was demonstrated that vagal nerve trunk denervation produced hyperalgesic behavior in normotensive rats. More direct evidence of vagal involvement with the perception of pain was demonstrated in rats using volume expansion with the plasma expander Ficoll. Right vagotomies were performed on experimental rats and sham operations involving exposing the right vagal nerve trunk were completed for controls. A third test group was given the opioid antagonist naltrexone prior to testing to evaluate endogenous opioid involvement. Infusion of a 5% solution of Ficoll was used for volume expansion and tail-flick response to aversive thermal stimuli was employed to assess antinociception. Volume expansion resulted in long lasting antinociception in all three groups. The vagotomized group demonstrated significant attenuation of antinociception compared to the sham or naltrexone treated groups (*Maixner and Randich 1984*).

A second experiment by the same investigators utilized foot-shock induced analgesia to assess right vagal nerve involvement in the nociception

expression. This method of stimuli involves both opioid and nonopioid mechanisms of pain. Attenuation of antinociception was observed for the foot-shock tested vagotomized rats. The outcomes of these two experiments indicate that the integrity of the right vagal nerve trunk is necessary for the full expression of antinociception induced by volume expansion as well as foot-shock induced analgesia.

The ability of cervical, thoracic, cardiac and diaphragmatic vagal afferent stimulation to modulate the digastric reflex in cats to tooth pulp-stimulation has been evaluated. The right maxillary tooth was stimulated and the right digastric muscle reflex recorded. Of the sites tested, cervical vagal stimulation produced a biphasic effect on the reflex dependent on the conditioning test interval. Cervical, cardiac and thoracic segments were all capable of producing inhibition of the reflex when tested. The results clearly indicate that cardiopulmonary vagal afferents inhibit the digastric reflex in cats (*Maixner, Bossut and Whitsel 1991*). In a later experimental study the effects of cardiac vagal electrostimulation was evaluated in regard to responses of trigeminal and trigeminothalamic neurons to orofacial thermal heat and non-noxious tactile stimuli in cats. In addition electrical stimulation of tooth pulp (Aδ or C fiber) and skin were tested. Cervical vagal afferent stimulation produced a predominantly inhibitory effect on the evoked responses of nociceptive neurons without regard of the source of convergent input projection site. This indicates that the cervical vagal stimulation is capable of altering nociceptive signals from deeper visceral structures as well as superficial cutaneous structures (*Bossut and Maixner 1996).*

Experimental and clinical evidence suggests an adaptive blood pressure and pain sensitivity relationship. Although the underlying mechanisms for hypertension hypoalgesia are not completely identified, some of the putative mechanisms involving baroreceptor activation, endogenous opioid mechanisms as well as vagus nerve stimulation have been discussed.

C. Pain Mechanisms in Endodontics

The trigeminal pain system is a multilevel system that is initiated by peripheral detection of tissue damaging stimuli followed by processing of that information at the level of the medullary spinal cord, and resulting in the perception of pain in the cerebral cortex (*Hargreaves et al 2006*). The cell bodies of most trigeminal primary afferents are located in the trigeminal ganglion. They terminate in the trigeminal brainstem sensory nuclear complex that is made up of the main sensory nucleus and the subnuclei oralis, interpolaris, and caudalis of the trigeminal spinal tract nucleus. The subnucleus caudalis is often referred to as the medullary dorsal horn. The medullary dorsal horn propagates the pain signal to the higher brain centers and also plays a role in the processing of the signal. The signal to the brain can be increased (hyperalgesia), decrease (analgesia), or be misread (referred pain). The major output pathway from medullary dorsal horn is through second order projection neurons to the thalamus via the trigeminothalamic tract. The thalamocortical tract continues the signal through third order neurons from the thalamus to the cerebral cortex where the perception of pain occurs (*Chiang et al 2011*, *Hargreaves et al 2006*).

Nociceptive endings present in the pulp and periapical tissues arise from A-δ fiber mechanoreceptors, and polymodal C-fibers, which transmit dull pain (*Johnsen 1985*). In addition, there are A-β mechanoreceptors which are discriminative touch receptors that normally encode only low frequency, non-noxious stimuli.

Peripheral sensitization occurs when the firing thresholds are lowered by repeated noxious stimuli resulting in changes in response patterns. With a reduction in firing thresholds there can be pain sensation to nonnoxius stimuli, allodynia, as well as increased pain response to noxious stimuli, referred to as hyperalgesia. In addition there can be spontaneous pain (*Fitzgerald and Woolf 1984; Hargreaves et al 2006; Matthews and Sessle 2008*). Response pattern changes are related to neurogenic inflammation and tissue injury that cause the release or activation of molecules involved with the sensitization of peripheral nociceptors. That includes the nociceptors enhanced release of substance P and calcitonin gene-related peptide. Other substances include cytokines, prostaglandins, nerve growth factor, histamine, bradykinin, serotonin, lipids, nitric oxide and hydrogen ions (*Hargreaves et al 2006, Henry and Hargreaves 2007*). As the process of inflammation continues the A-β fibers will begin signaling pain, adopting characteristics of C-fibers, which is a form of allodynia (*Merrill 2007*).

Central sensitization is defined as increased synaptic efficiency established in nociceptive neurons in the dorsal horn of the spinal cord following intense peripheral noxious stimuli, tissue injury, or nerve damage (*Xie 2008).* This contributes to amplification of the noxious input and spread of pain outside the original damaged region (hyperalgesia) and the onset of pain from normally innocuous stimuli (allodynia) (*Fitzgerald and Woolf 1984*). The process proceeds due to a nociceptive afferent barrage

of chemical mediators that include glutamates and neuropeptides such as substance P and calcitonin-gene related peptide. These mediators prolong depolarization of the neurons and increase their excitability via glutamate and G-protein coupled receptors (*Sessle et al. 2008*).

There is growing evidence that glial cells (microglia and astrocytes) are activated by inflammation of peripheral nerve injury and are involved in spinal nociceptive transmission and central sensitization. Sensitization of neurons in the trigeminal subnucleus caudalis in the medullary dorsal horn is not only indirect via release of cytokines and tumor necrosis factor but also directly from the release of glutamate (*Xie et al. 2007; Xie 2008*).

D. Postoperative Pain in Endodontics

Pain is an unpleasant sensory and emotional experience that is associated with either actual or potential tissue damage, or is described in terms of such damage (*International Association for the Study of Pain 1979*). Achieving pain control in an effective and predictable manner is an important aspect of endodontic therapy. This includes both intra- and postoperative pain. The incidence of pain in the immediate postoperative period (ie.1-7 days) ranges from 8.3% to 62% (*Seltzer and Bender 1961; Fox et al 1970; Mulhern et al 1982, Georgopoulou et al 1986;Sathorne et al 2007)*. The incidence of persistent postoperative several months (12 -59 months) after completion of NSRCT has been reported to be as high as 12% (*Polycarpou et al 2005*).

In 1983 a clinical study was conducted to determine factors associated with increased incidence of pain or pain intensity associated with nonsurgical root canal

therapy for 229 asymptomatic patients. Interappointment pain was recorded as none, slight, or moderate to severe. Slight was defined as pain of brief duration not requiring medication for relief. Moderate to severe was defined as pain that required medication or other palliative treatment. Risk factors evaluated were tooth arch location, number of roots of the teeth, previous emergency treatment, presence of a periapical radiolucency, and pulp vitality status determined by clinical observation not vitality testing. The results were that 55.5% of subjects experienced no interappointment pain, 28.8% reported slight pain, 15.7% reported moderate to severe pain. Additionally, no significant correlation was found for any of the risk factors evaluated (*Harrison et al, 1983*). In a similar study, 245 patients were treated by undergraduate dental students and risk factors evaluated were pulp vitality with testing, presence of periapical radiolucency, previous treatment, over-instrumentation at any stage of treatment, type of anesthetic used, sex, age, and tooth type. After instrumentation procedures 43% of patients reported pain; 21% had slight pain, and 22% had moderate to severe pain. Of the risk factors evaluated, over-instrumentation at the apex had a significant correlation with incidence and degree of postoperative pain (*Georgopoulou et al, 1986*).

Many factors have been evaluated for predictors of post-operative pain. Preoperative pain and preoperative apprehension have been found to be significant risk factors for postoperative pain (*Torabinejad et al 1994*). In that study 588 patients with varying degrees of pre-operative pain underwent complete instrumentation of the root canal system and their pain severity was assessed using a visual analog scale for 72 hours after treatment. Pre-operative pain intensity was positively correlated with post-operative pain intensity. Thus postoperative pain continues to be difficult to predict and manage.

INTRODUCTION

Effective pain control in both pre- and postoperative phases is an important aspect of endodontic therapy. Pain incidence in the immediate post-operative period (ie.1-7 days) ranges from 8% to 62% (*Seltzer and Bender 1961; Fox et al 1970; Mulhern et al 1982, Georgopoulou et al 1986; Sathorn et al 2008).* The incidence of persistent post-operative several months (12 -59 months) after completion of nonsurgical root canal therapy has been reported to be as high as 12% (*Polycarpou et al 2005*). While some of the factors which affect pain resolution after endodontic therapy have been identified, it is yet to be demonstrated whether preoperative arterial blood pressure affects the resolution of postoperative pain.

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Hypertension hypoalgesia is not exclusive to experimental pain as evidenced by data collected in the Nord-Trondelag Health Survey (*Hunt 1 and Hunt)* Data from these surveys reported that individuals with high blood pressure have a lower prevalence of chronic musculoskeletal complaints as compared to those with normal blood pressure (*Hagen et al 2004*). More recently Tronvik et al (2008) reported that increased arterial blood pressure was associated with a decreased prevalence of migraine and nonmigrainous headaches. However, these studies have not addressed odontogenic pain.

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Based on the preclinical and clinical evidence supporting hypertension hypoalgesia we conducted a prospective observational study to evaluate the relationship between resting arterial blood pressure and postoperative pain associated with endodontic treatment. We hypothesized that resting arterial blood pressure is inversely correlated to decreased postoperative pain in endodontic patients. We found a significant inverse correlation between preoperative systolic blood pressure and postoperative pain Day 1 ($p=0.03$). Additionally we found an inverse correlation between preoperative pulse pressure and postoperative day 1 pain ($p=0.005$). Our results provide further evidence that there is a functional interaction between cardiovascular and pain regulatory systems. Increasing our understanding of how the human body naturally modulates and regulates pain will enhance our ability to prevent and manage pain associated with endodontic therapy.

MATERIALS AND METHODS

A. Subjects

This protocol was approved by the University of North Carolina Institutional Review Board. This was a prospective study. Patients were recruited from the University of North Carolina School of Dentistry Graduate endodontic clinic. All subjects were English-speaking, between 18 and 70 years old, and required root canal therapy. Subjects' pulpal diagnosis was limited to pulpal necrosis as determined by lack of response to cold (dichlorodifluoromethane, Endo Ice; HYGENIC®, Akron OH) and electric pulp tester (Sybron Endo Vitality Scanner Model 2006, Glendale, CA). Clinical periradicular diagnosis was limited to periradicular periodontitis as determined by the presence of periradicular radiolucency more than twice the width of the periodontal ligament and/or sensitivity to percussion. Subjects were enrolled regardless of preoperative pain level reported. Exclusion criteria included American Society of Anesthesiologists' physical status of 3 to 5, a periodontal pocket greater than 6 mm around the tooth to be treated (to exclude potential perio-endo lesions), and persistent (>7 days) use of medication that might alter their pain report (such as steroids and antidepressants). Written informed consent was obtained and subjects were asked to complete pre-treatment questionnaires. Physiologic parameters including vital signs (blood pressure, heart rate) were recorded.

B. Experimental Protocol

Pretreatment questionnaires were completed by subjects. The subject was asked to answer questions regarding demographics, history of pain with the affected tooth, as well as presence or absence of any orofacial and/ or chronic pain indicated by drawing on a picture of a manikin from the front and back views.

A standardized root canal therapy was initiated in the University of North Carolina endodontic graduate or undergraduate clinic. Local anesthetic was administered; rubber dam isolation was achieved; access to the pulp chamber established and working length radiographs were obtained; canals were instrumented using nickel-titanium rotary and stainless steel hand instruments up to a minimum apical International Organization for Standardization size 35 with 0.04 taper. Additionally, calcium-hydroxide was placed as an interappointment medicament. The appropriate temporary restoration was placed and a second appointment was made to complete the root canal procedure. Patients were informed of the possibility of post operative pain following the procedure and provided with written post operative instructions. Patients were then asked to complete a seven day post operative pain diary based on their level of worst pain and average pain for seven consecutive days after treatment as well as a question related to mechanical allodynia. No analgesics were prescribed but subjects were asked to report any self medication that occurred post operatively including dosage and frequency. Patients were given an addressed, stamped envelope to mail the pain diary back to the investigators after completion.

C. Questionnaires

Subjects completed a series of forms including general demographic data and a medical history questionnaire, a consent form, and the questionnaires described below:

a. Pretreatment subject questionnaires (Appendix A) were completed while sitting in the dental chair prior to root canal therapy being initiated. The patient was asked to answer questions regarding demographics, history of pain with the affected tooth, as well as presence or absence of any orofacial or chronic pain indicated by drawing on a picture of a manikin from the front and/or back views. A 100mm horizontal Visual Analog Scale (VAS) with the anchors "No pain" and "Worst pain imaginable "were used to assess pain (*Seymour 1982; Katz and Melzack 1999*).

b. Preoperative provider questionnaires (Appendix B) were completed by the dentist providing treatment after diagnosis and prior to initiation of treatment. Providers were instructed to record the tooth number, pulpal and periapical diagnosis, etiology, VAS for cold testing and percussion, periodontal probing, whether the tooth was in occlusion and if there were missing adjacent teeth.

c. Postoperative pain diaries (Appendix C) assessed the subject's pain experience up to seven days after treatment. Subjects were instructed to complete the questionnaire at the same time everyday and record that time. They were also asked to rate the worst pain and average pain they felt in the teeth or mouth during the past 24 hours on a 100mm horizontal VAS. In addition, mechanical allodynia was assessed using a yes or no response to pain related to having the patient tap on the treated tooth with their finger. Medication intake was also assessed

including whether or not medication was taken to relieve pain, the name of the medication, dosage in milligrams were recorded.

D. Sample Size Calculations:

Using SAS® v9.2 proc power we calculated that a comparison between 35 patients with above-median visual analog scale (VAS) pre-operative pain and 35 patients with below-median VAS pain would have 80% power to detect relative risks ranging from 2.6 (if incidence of post-operative pain were 20%) to 3.8 (if incidence were 10%). For the same sample of 70 patients, power would reduce to between 21% (10% incidence) and 44% (20% incidence), if relative risk were only 2.0, although that would still be sufficient for planning the large-scale study. Assuming that 70% of subjects return completed diaries, we therefore propose to recruit a total of 100 patients for this study.

E. Statistical Analysis:

Data from examination, questionnaires and follow-up diaries were merged to produce an analytic data file in which each person will represent one unit record. SAS® v9.2 (SAS Institute, Cary NC) was used to estimate postoperative pain intensity and associated 95% confidence intervals for the complete cohort. Patients were classified according to preoperative and postoperative VAS ratings and dichotomized at the median value. Contingency tables were used to estimate relative risk for postoperative pain and 95% confidence intervals associated with each risk factor. Stratified analyses investigated potential confounding or effect modification of the primary risk factor (preoperative VAS

pain). Fully adjusted estimates for all risk factors identified in the preceding steps were evaluated in a multivariable log-binomial regression model.

RESULTS

A. Group Profile

All patients recruited for this investigation presented to the University Of North Carolina School Of Dentistry for root canal therapy by undergraduate students or graduate endodontic residents. Ninety-three subjects were enrolled. Twenty subjects did not return their post operative pain diaries so their data was not included for comparison. This resulted in seventy-three completed entries. Table 1 displays the demographics of the seventy-three subjects enrolled in this study. Twenty-six (36%) of subjects were males and forty-seven (64%) were females. The mean age of subjects was 46 ± 15 years. The age range for subjects was 18 to 70 years. The majority of participants were Caucasian (63%).

Seventy-three subjects (100%) were diagnosed with periradicular disease. Sixty-three subjects (86%) had a periapical radiolucency present on the preoperative radiograph. Thirty subjects (41%) were diagnosed with symptomatic apical periodontitis and another eight subjects (11%) were diagnosed with apical periodontitis with abscess. Thirty subjects (41%) were diagnosed asymptomatic apical periodontitis followed by five subjects (7%) diagnosed with chronic apical abscess. Table 2 shows the distribution of the teeth treated. Thirty molars (41%), twenty-three premolars (31%) and twenty anterior teeth (28%) were endodontically treated in the study.

B. Preoperative Blood Pressure, Pain and Mechanical Allodynia Characteristics

Physiologic data is presented in Table 3. The overall mean systolic blood pressure was 126 $\pm$ 16 and the mean diastolic blood pressure was 78 $\pm$ 10. Mean heart rate was 72.0 $\pm$ 9 beats/minute. Mean pulse pressure was 48 $\pm$ 12 and the average mean arterial blood pressure was 93 $\pm$ 10. None of the subjects were taking medication for hypertension.

Thirty eight subjects (52%) reported preoperative pain at the time of enrollment Table 4. The mean pain intensity level using a 100mm horizontal VAS was 52 $\pm$ 31. In addition, twenty seven of the thirty eight subjects (71%) that reported preoperative pain also reported mechanical allodynia. We did not find a significant association between pretreatment pain and any of the baseline demographic variables including subject age, gender, race, tooth type treated, arch location, and presence of orofacial pain, bodily pain, or headache.

C. Postoperative Pain Levels Mechanical Allodynia and Analgesics

The course of mean postoperative endodontic pain is shown in Table 4. Seventy-five percent of subjects (n=55) reported pain on Day 1 postoperatively with a mean VAS of 24 ± 26. Reported mean worst pain intensity decreased gradually over the seven day period with a mean VAS of 3 ± 8 by Day 7. Thirty-four (90%) of the thirty-eight subjects that reported preoperative pain also reported pain Day 1 postoperatively. Table 4 also shows presence of mechanical allodynia over the seven days postoperatively. Forty six percent (n=34) of subjects reported mechanical allodynia by tapping a finger on the treated tooth on Day 1. Sixty-five percent of those thirty four subjects (n=22) had

reported mechanical allodynia to finger tap pain preoperatively. Presence of mechanical allodynia decreased gradually over the seven days but still remained for fifteen percent (n=11) of subjects on Day 7. Thirty-four subjects (39%) reported taking oral analgesics for postoperative pain on Day 1. At Day 4 fourteen subjects (19%) reported taking pain medication and seven patients (10%) were taking analgesics on postoperative Day 7. Ibuprofen was the most frequently used analgesic. None of the demographic characteristics were found to be associated with mean Day 1 worst pain or average pain scores including subject age, gender, race, tooth type treated, arch location, and presence of orofacial pain, bodily pain, or headache.

D. Correlations

Fit and ordinary linear transgression model was used to predict postoperative VAS intensity with preoperative pain and blood pressure values as covariates. Pearson correlations were performed to assess the relationship between the measures of postoperative pain and preoperative blood pressure variables. We found a significant inverse correlation between preoperative systolic blood pressure and post instrumentation pain Day 1 ($p=0.03$). Additionally we found an inverse correlation between preoperative pulse pressure and post instrumentation Day 1 pain ($p=0.005$). Table 3 shows the preoperative systolic blood pressure and pulse pressure characteristics as well as postoperative Day 1 pain intensity characteristics. Figure 1 demonstrates the scatter plot graph of mean Day 1 VAS pain and preoperative systolic blood pressure. Figure 2 illustrates, by scatter plot graph, the mean Day 1 VAS pain intensity as compared to preoperative pulse pressure measurements.

DISCUSSION

Our objective in this study was to compare postoperative pain intensity outcomes of patients with different preoperative blood pressure characteristics using standardized clinical protocols. Our study design had the advantages of prospective studies. It provided an efficient method of investigating potential associations between a disease and associated factors and it was less prone to observer and respondent biases. Other advantages were that we were allowed a direct method of evaluating disease incidence and the time sequence of events was consistent with the natural history of disease development (*Torabinejad et al. 1994*).

This is the first study specifically designed to evaluate preoperative blood pressure characteristics as a predictor for postoperative pain for endodontic patients. The present investigation is in agreement with previous laboratory and clinical pain research that there is an association between increased resting blood pressure and a decreased pain perception *(Zamir and Segal 1979; Zamir, Simantov and Segal 1980; Naranjo and Fuentes 1985; Zamir and Shuber 1980; Ghione et al 1988; Sheps et al 1992).* Furthermore, our study provided further evidence that the blood pressure and pain relationship extends beyond experimental pain scenarios and is recognized in post operative pain. In agreement with a previous postsurgical study, our study demonstrated that preoperative resting systolic blood pressure is inversely correlated with postoperative pain (*France and Katz 1999*).

The present study was limited in that blood pressure measurements were recorded only once preoperatively. Additionally there was not a standardized protocol for taking blood pressure measurements. This limitation could reflect potential reliability issues with the blood pressure measurements. Although our study observed similar blood pressure and pain relationships found in controlled laboratory conditions, future studies should include a more strict protocol for blood pressure measures. This would include using one calibrated and reliable devices for blood pressure measurements as well as having several measurements taken preoperatively, during treatment and postoperatively. Heart rate variability monitoring would be a useful measure to be able to measure the balance of sympathetic and parasympathetic mediators of heart rate (*Reed et al 2005; Chapleau and Sabharwal 2010*). For future studies this would have the added benefit of being able to evaluate the baroreceptor reflex as well cardiovagal activity.

In this study our pain intensity ratings for subjects were recorded at a single time for each postoperative day. Additional pain rating at several times throughout the day would allow better insight into the waxing and waning of postoperative pain. Pain incidence in the immediate post-operative period (ie.1-7 days) ranges from 8% to 62% (*Seltzer and Bender 1961; Fox et al 1970; Mulhern et al 1982, Georgopoulou et al 1986;Sathorn et al 2008).* In the present study the incidence and intensity of pain after nonsurgical root canal treatment reached its maximum within the first day after treatment when seventy-five percent of subjects (n=55) reported pain with a mean VAS of 24 ± 26. The present study likely has insufficient power to detect differences between subjects that had no history of orofacial pain, chronic bodily pain or headache and those with a positive history for any of those conditions.

Our results provide further evidence that there is a functional interaction between cardiovascular and pain regulatory systems that exists postoperatively. The present study is in agreement with other postoperative pain findings with regard to a negative correlation between preoperative systolic blood pressure and post operative pain (*France and Katz 1999*). This is the first study to identify an association between pulse pressure and post operative pain. This association requires further investigation with strict protocols and broader blood pressure measures to confirm the results of this study.

This study's results are clinically relevant to hypertension as a disease clinical pain management and prevention. Based on current evidence, hypoalgesia has been suggested to correlate with deregulation of central nervous system structures involved with both cardiovascular and pain regulatory systems in individuals that are genetically predisposed to this disease. Clinically, hypoalgesia may serve as a marker to identify patients at greatest risk for hypertension (*France 1999*). The negative correlation between blood pressure and pain has not been found with subjects that have chronic orofacial or chronic bodily pain (*Maixner 1997, Bruehl 2002*). Thus it is important to identify these patients as they may be more at risk for more intense or longer lasting pain. It is imperative to continue this line of research in order to increase our understanding the body's natural modulation and regulation of pain. This knowledge will enhance our ability to prevent and manage pain associated with endodontic therapy.

Appendix A

Patient Pain Survey

We would first like to collect information about the tooth being treated <u>today</u>. Please answer the following questions about your tooth.

1. **Do you have any pain in the tooth being treated today?**

   Yes..... ☐ 1

   No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 7**

2. **How long have you had pain in the tooth being treated today?**

   Less than 1 week..... ☐ 1

   1-3 weeks..... ☐ 2

   More than 3 weeks..... ☐ 3

3. **Please place an "X" on the line to indicate the amount of pain you felt today in this tooth before you saw the dentist.**

   No _____ **Worst Pain**

4. **Please place an "X " on the line to indicate th . that you have ever had in this tooth.**

   No _____ **Worst Pain**

5. **Have you taken any pain medications in the p**

   Yes..... ☐ 1

   No..... ☐ 2

6. **Does your tooth hurt (or hurt <u>more</u>) if you tap on it with your fingernail?**

   Yes..... ☐ 1

   No..... ☐ 2

The following questions are about pain and other symptoms in your face. For our purposes, face refers to your temples, cheek, jaw, muscles, ears, or jaw joints. Jaw joints mean the part of your face in front of your ear that moves when you open and close your mouth. Please note that the following questions do not refer to your toothache.

7. **In the past year, have you ever had pain in your face, jaw, temple, in front of the ear, or in the ear, not including toothache or ear infection?**

   Yes..... ☐ 1

   No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 11**

8. **How many months or years ago did your facial pain begin?**
   _____ months OR _____years

9. **How would you describe your facial pain?**

   Persistent – continuous pain since initial onset..... ☐ 1

   Recurrent – more than one bout of pain, with periods of no pain..... ☐ 2

   One time – a prior episode that has ended..... ☐ 3

10. **In the past year, how intense was your worst facial pain? Please place an X on the line to indicate the intensity.**

    |——————————————————————|
    No Pain **Worst Pain**

11. **In the past year, have you had any headaches**

    Yes..... ☐ 1

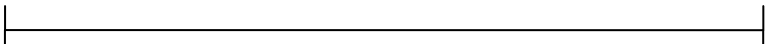
    No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 14**

12. **In the last 30 days, how many headaches of any type (for example stress or tension-type, migraine, hunger headache, sinus headache) have you had?**

_____ **Number of headaches in the last 30 days**

☐ **No headaches in the last 30 days**

13. What is the worst intensity of this headache during the last 30 days? Please place an X on the line to indicate the intensity.



No **Worst Pain**

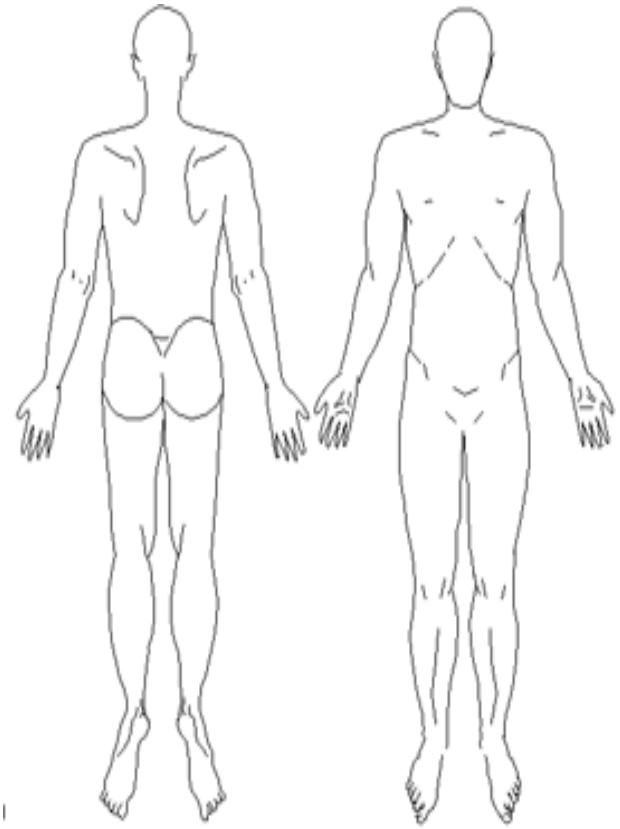
We are interested in <u>other body</u> pains you may have experienced that lasted a day or more, or that have occurred several times a year due to any cause. Please do not report aches and pains that are fleeting or minor such as sore muscles after exercising.

14. In the last year have you had a persistent or chronic pain in any areas <u>other</u> than your face?

Yes..... ☐ 1

No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 17**

15. **On the figure below please shade in the areas where you have this <u>body</u> pain.**



16. **In the past year, how intense was your worst <u>body</u> pain? Please place an X on the line to indicate the intensity.**

No **Worst Pain**

Please complete the following questions to tell us [illegible] about yourself. You may refuse to answer any question. As a reminder, all information you provide is confidential.

17. **What is your age?**

_____ years

18. **What is your sex?**

Male..... ☐ 1

Female..... ☐ 2

19. Are you of Hispanic or Latino origin?

Yes..... ☐ 1

No..... ☐ 2

20. What is your race?

American Indian/Alaskan Native..... ☐ 1

Asian..... ☐ 2

Black/African American..... ☐ 3

Native Hawaiian/Other Pacific Islander..... ☐ 4

White..... ☐ 5

Other (please specify:_____ _____) ☐ 6

21. What is the highest grade or level of schooling that you have completed?

Less than 8 years..... ☐ 1

8-11 years..... ☐ 2

12 years or completed high school or GRE..... ☐ 3

Post high school training other than college..... ☐ 4

Some college or 2-year college degree..... ☐ 5

4-year college degree..... ☐ 6

Post graduate level..... ☐ 7

22. Are you covered by health insurance or some other kind of health care plan? Please include health insurance obtained through employment or purchased directly as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.

Yes..... ☐ 1

No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 24**

23. What kind of health insurance or health care coverage do you have? Please check all that apply

Private health insurance (for example through an employer, COBRA or a policy you obtained yourself)..... ☐ 1

Medicare, Medi-gap, Medicaid, Military health care, VA, CHAMPUS/TRICARE/CHAMP-VA or State-sponsored health plan..... ☐ 2

24. Which of the following describes you?

Current smoker..... ☐ 1

Former smoker..... ☐ 2

I've never been a smoker..... ☐ 3

THANK YOU FOR COMPLETING THIS SURVEY. PLEASE STOP NOW AND RETURN THIS DOCUMENT TO THE PERSON WHO GAVE IT TO YOU.

Appendix B

TO BE COMPLETED BY THE DENTIST PROVIDING ENDODONTIC THERAPY

D1. Tooth # _____

D2. Pulpal diagnosis: (Please mark only one)

Healthy pulp..... ☐ 1

Irreversible pulpitis (do not include those with iatrogenic carious exposure)..... ☐ 2

Necrotic pulp..... ☐ 3

Previous pulpotomy..... ☐ 4

Previous RCT..... ☐ 5

D3. Periapical diagnosis: (Please mark only one)

Normal..... ☐ 1

Acute Apical Periodontitis..... ☐ 2

Chronic Apical Periodontitis..... ☐ 3

Acute Exacerbation of CAP..... ☐ 4

Apical periodontitis with abscess (APA)..... ☐ 5

Apical periodontitis with sinus tract (APST)..... ☐ 6

Sclerotic apical periodontitis (SAP)..... ☐ 7

D4. Etiology: (Mark all that may apply)

Caries..... ☐ 1

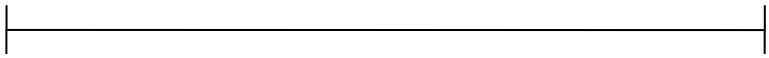
Mechanical exposure..... ☐ 2

Restorative necessity..... ☐ 3

Trauma..... ☐ 4

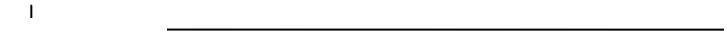
D5. Please mark an X on the line to rate the patients' response to:

a. Cold test



No response — **Most extreme response**

b. Perc



No response — **Most extreme response**

D6. PPD: _____ mm

D7. Is the tooth being treated today in occlusion?

Yes..... ☐ 1

No..... ☐ 2

D8. Are any adjacent teeth missing?

Yes..... ☐ 1

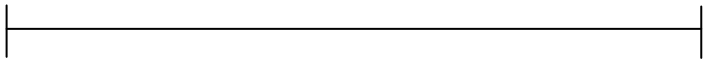
No..... ☐ 2

Appendix C

ID _____

Date ____/____/_____ **Time** ___:___ ☐ **am** ☐ **pm**
Day Month Year

1. **Please place an "X " on the line to indicate the worst pain that you had in your tooth today.**



2. **Have you taken any pain medications today?**

Yes..... ☐ 1

No..... ☐ 2 ➡ **IF NOT, GO TO QUESTION 4**

3. **Please tell us the name, dose and number of pain medications you took today.**

_____ **Name** (for example, Advil, Tylenol, Motrin, etc.)
_____ **Number**
_____ **Dose**

4. **Does your tooth hurt (or hurt <u>more</u>) if you tap on it with your finger nail?**

Yes..... ☐ 1

No..... ☐ 2

5. **Have you had any other treatment done on your tooth since your root canal treatment?**

Yes..... ☐ 1

No..... ☐ 2

Table 1: Demographics of Enrolled Subjects

Sex	**N***	**(%)**
Male	26	(36)
Female	47	(64)
Race	**N***	**(%)**
American Indian/ Alaskan Native	2	(3)
Asian	4	(5)
African American	13	(18)
Native Hawaiian/ Pacific Islander	2	(3)
Caucasian	46	(63)
Other	6	(8)

***Total N = 73 subjects**

Table 2: Tooth Type Treated of Enrolled Subjects

Tooth Type	**Anterior**		**Premolar**		**Molar**	
	N*	**(%)**	**N**	**(%)**	**N**	**(%)**
Maxillary	13	(18)	19	(26)	19	(26)
Mandibular	7	(10)	4	(5)	11	(15)

***Total N = 73 teeth**

Table 3: Blood Pressure Characteristics of Enrolled Subjects

BP Value	Minimum	Maximum	Mean	Standard Deviation
Systolic	**94**	**167**	**126**	**16**
Diastolic	**60**	**95**	**78**	**10**
Heart Rate	**47**	**103**	**72**	**9**
Pulse Pressure	**20**	**82**	**48**	**12**
Mean Arterial Pressure	**73**	**118**	**93**	**10**

Table 4: Pre and Postoperative Pain Intensity and Mechanical Allodynia for Enrolled Subjects

Time to Instrumentation	Pain Frequency (Percent)	Min VAS	Max VAS	Mean VAS	SD	Mechanical Allodynia Frequency (percent)
Preoperative	38 (52)	2	100	52	31	38 (52)
Day 1 pain *	55 (75)	1	84	24	26	34 (46)
Day 2 pain *	53 (73)	1	89	21	26	30 (41)
Day 3 pain *	47 (64)	1	97	15	23	23 (32)
Day 4 pain *	42 (58)	1	88	10	19	18 (25)
Day 5 pain *	32 (44)	1	64	5	10	16 (22)
Day 6 pain *	35 (48)	1	55	4	9	11(15)
Day 7 pain *	29 (40)	0.80	40	3	8	11 (15)

Table 5: Preoperative Systolic Blood Pressure , Pulse Pressure and Day 1 Postoperative Pain Intensity for Enrolled Subjects

Variable	N	Minimum	Maximum	Mean	Standard Deviation
Pre-op Systolic	73	94	167	126	15.77
Pre-op Pulse Pressure	73	20	82	48	12.44
VAS Day 1	73	1	84	24	26.12

Figure 1: Day 1 Postoperative Pain Intensity and Preoperative Systolic Blood Pressure for Enrolled Subjects

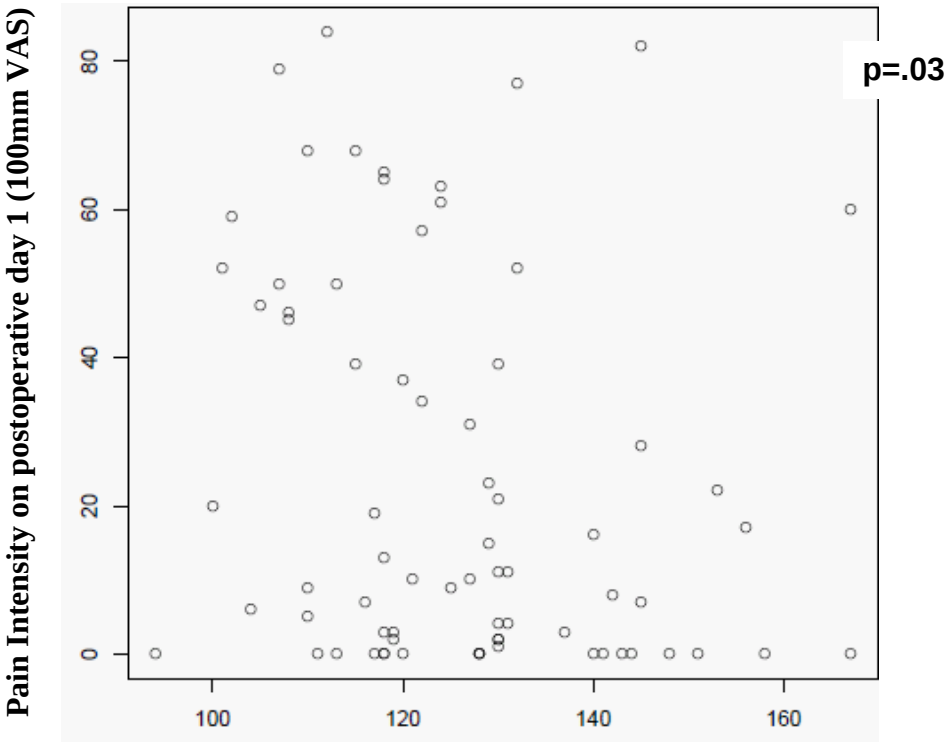
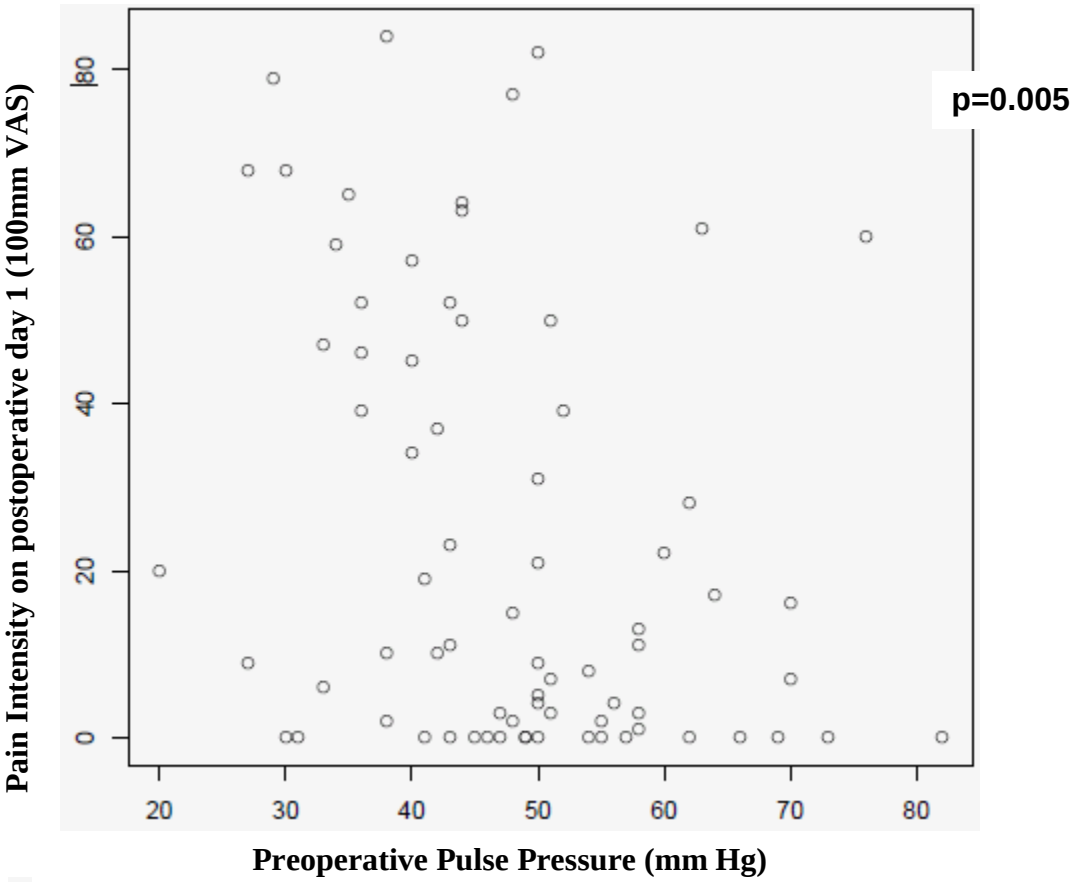


Figure 2: Day 1 Postoperative Pain Intensity and Preoperative Pulse Pressure for Enrolled Subjects



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