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ated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this burden to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	Aug 94	

4. TITLE AND SUBTITLE
The Ablation or Reduction of Intraoperative Tourniquet Pain with Preoperative Administration of IV Ketorolac Tromethamine

5. FUNDING NUMBERS

6. AUTHOR(S)
Timothy J. Samolitis

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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Loyola University

8. PERFORMING ORGANIZATION REPORT NUMBER
AFIT/CI/CIA
94-117

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
DEPRTMENT OF THE AIR FORCE
AFIT/CI
2950 P STREET
WRIGHT-PATTERSON AFB OH 45433-7765

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

DTIC ELECTE AUG 19 1994 S G D

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for Public Release IAW 190-1
Distribution Unlimited
MICHAEL M. BRICKER, SMSgt, USAF
Chief Administration

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

14. SUBJECT TERMS

15. NUMBER OF PAGES
84

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT

DTIC QUALITY INSPECTED 1

94-117

The Ablation or Reduction of Intraoperative Tourniquet Pain with Preoperative Administration of IV Ketorolac Tromethamine

A research paper submitted in partial fulfillment of the requirements for the degree of Master of Science at Virginia Commonwealth University

by

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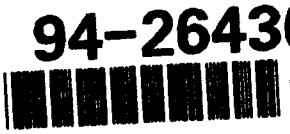
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This is to certify that the research paper prepared by Timothy J. Samolitis entitled: THE ABLATION OR REDUCTION OF INTRAOPERATIVE TOURNIQUET PAIN WITH PREOPERATIVE ADMINISTRATION OF IV KETOROLAC TROMETHAMINE has been approved by his committee as satisfactory completion of the research paper requirement for the degree of Master of *Science in Nurse Anesthesiology*.

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29 June 1994
Date

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Acknowledgements

I wish to express my love and gratitude to my wife and fellow classmate, Kelly, who provided me with support and words of encouragement throughout this long endeavor. Her efforts in this project of proofreading and recommendations are greatly appreciated.

Also, I wish to thank my mother, Frances, extended family and friends, who always encouraged me to strive for my best effort. It is with heartfelt appreciation that I dedicate this research paper to my late father, Anthony, who sacrificed much to support my education.

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Introduction

The application of tourniquets on upper or lower extremities is frequently used by surgeons to provide a clear operative field while minimizing blood loss. These are attractive benefits for utilization of tourniquets, however consequences do exist. The release of prostaglandins by injured cells in response to tourniquet compression increases pain perception. This occurs by prostaglandins sensitizing and exciting pain receptors. The purpose of this research is to determine the efficacy of a preoperative dose of ketorolac tromethamine, given prior to tourniquet inflation for orthopedic surgery, to maintain baseline heart rate and blood pressure values. Ketorolac tromethamine, a nonsteroidal antiinflammatory drug, has physiologic action based upon prostaglandin reduction. It acts peripherally by inhibiting the enzyme cyclooxygenase which converts arachidonic acid to prostaglandins (Stoelting, 1991).

Preoperative intravenous administration of ketorolac tromethamine assures that the medication reaches its peripheral site of action prior to circulatory occlusion by a tourniquet. Conceivably, a diminished pain response associated with tourniquet compression is observed with

prostaglandin reduction. Presently, there are no published studies utilizing ketorolac tromethamine in this manner.

Purpose

The purpose of this research is to evaluate whether ketorolac tromethamine, a nonopioid, peripherally acting analgesic, when given preoperatively, might ablate or significantly reduce intraoperative tourniquet pain in orthopedic procedures.

Statement of the Problem

Can preoperative administration of ketorolac tromethamine ablate or significantly reduce the intraoperative nociceptive reaction to tourniquet pain?

Hypothesis

Preoperative ketorolac tromethamine intravenous administration will have no significant effect in reducing or ablating the intraoperative nociceptive reaction to tourniquet pain.

Variables

Independent Variable. Preoperative ketorolac tromethamine administration is the independent variable.

Dependent Variables. The dependent variables are maintenance or reduction of preoperative blood pressure and heart rate values.

Assumptions

1. The experimental groups are randomized.

2. A placebo of normal saline has no intrinsic drug effects.

3. The onset of tourniquet pain is not associated with tourniquet width or level of pressure applied to the pneumatic tourniquet.

4. Tourniquet pain and tourniquet hypertension arise from the same cause.

Limitations

1. Depth of anesthesia between individuals varies depending upon their response to and metabolism of anesthetic agents.

2. The anesthetic technique during induction and maintenance varies between providers.

Delimitations

1. An urban Level I trauma center based in the mid-Atlantic region with 1,052 beds is used as the single patient population sample for data collection.

2. The study is limited to patients between 18 and 65 years of age that are without disqualifying health conditions as stated in the methodology.

3. The study is confined to patients undergoing orthopedic surgery requiring application of a tourniquet for at least one hour.

4. Collection of data for the study is completed within three months.

Definition of Terms

Adrenergic. The term adrenergic pertains to epinephrine or norepinephrine, the hormone and neurotransmitter of the adrenal medulla and postganglionic sympathetic nervous system.

Afferent. The term afferent pertains to an "inward flow" from the periphery towards a central point such as the inward transmission of sensory nerve impulses to the spinal cord or brain.

A-delta fiber. The A-delta fiber is a myelinated nerve fiber associated with transmitting pain that is immediate, sharp, and localized in response to injury.

Algogenic mediator. An algogenic mediator is a substance which sensitizes or excites pain receptors (nociceptors) and acts as a mediator of inflammation.

Agonist. An agonist is a ligand that binds to a plasma membrane receptor and induces a physiologic response.

Amygdala. The amygdala is that portion within the brain that contributes an affective influence refered to as "mood," in relation to sensory input.

Arachidonic acid. Arachidonic acid is an obligatory precursor of prostaglandins.

ASA. The ASA is a five-category physical status classification system adopted by the American Society of Anesthesiologists in 1961 to assess a patient's preoperative status for anesthetic planning and management.

Axon. An axon is a long fiber-like structure that extends from the cell body of a nerve to make contact with other nerve cells.

Baroreceptor. A baroreceptor is a specialized receptor to detect and mediate changes in blood pressure.

C-fiber. The C-fiber is a nonmyelinated nerve fiber associated with the second, slower transmission of pain following injury. The pain is considered to be a dull, burning, achy, diffuse, and extremely unpleasant sensation.

Cholinergic. The term cholinergic pertains to acetylcholine, the sole neurotransmitter of the pre- and postganglionic parasympathetic nervous system.

Cortex. The cortex pertains to the outer part of an organ, such as the cortex of the brain.

Cyclooxygenase. Cyclooxygenase is an oxidative enzyme that converts arachidonic acid to prostaglandins.

Dorsal horn. The dorsal horn pertains to the posterior half of the gray matter within the central nervous system.

Double-blind study. A double-blind study is an experiment in which neither the experimenter nor subjects involved in the experiment know who is in the study or control groups.

Ectoderm. Ectoderm refers to the outermost layer of the primitive germ layers of the embryo. The epidermis and epidermic tissues, such as the finger or toe nails, hair, glands of the skin, nervous system, external sense organs (eyes, ears, etc.) and mucous membranes of the mouth and anus are derived from the ectoderm.

Efferent. The term efferent pertains to the "outward flow" from a central point, as in transmission of nerve impulses from the brain or spinal cord to the periphery.

Endorphins. Endorphins are a variety of endogenous peptides with morphine-like qualities located in the brain. These peptides act upon opioid receptors found on the surface of certain central nervous system (CNS) neurons.

Epinephrine. Epinephrine is a catecholamine and chief hormone of the adrenal medulla that stimulates the sympathetic nervous system. Epinephrine is also known as adrenaline and acts with norepinephrine to prepare the body for a "fight or flight" response.

Ergotropic. The term ergotropic pertains to the sympathetic nervous system which functions to mobilize and expend energy (ergo = energy; trophos = releasing).

Ganglion. A ganglion is a group of nerve cell bodies often located outside the central nervous system. The parasympathetic ganglia are located in or near organs being innervated. The sympathetic ganglia are arranged on either side of the spinal cord in chain-like fashion.

Gray matter. Gray matter is that portion of the central nervous system composed of nerve cell bodies, dendrites, and the proximal and terminal unmyelinated portions of axons.

Hypothalamus. The hypothalamus is that portion of the brain that regulates the pituitary gland, autonomic nervous system, emotional response, body temperature, water balance, and appetite.

Internuncial neurons. Internuncial neurons are regulatory neurons that comprise a network between sensory, motor, and other interneurons of the nervous system.

Kappa receptor. The kappa receptor is one of five opioid receptors associated with sedation.

Laminae. The laminae pertain to nine separate layers of gray matter that make up the lateral, medial, and dorsal horns within the spinal cord.

Leukotrienes. Leukotrienes are derivatives of arachidonic acid and are important mediators of inflammation

and allergic reactions by a synergistic action with other mediators such as histamine.

Ligand. A ligand is a compound that can bind with a high degree of specificity to a receptor.

Limbic system. The limbic system is the prefrontal cortex, hippocampus, amygdala, and hypothalamus portions of the brain that collectively function to control emotional and behavioral patterns.

Lipoxygenase. Lipoxygenase is an enzyme that catalyzes the reaction of oxygen with arachidonic acid and other polyunsaturated fatty acids into the leukotrienes.

MAC. MAC refers to the minimum alveolar concentration of an inhaled anesthetic that prevents movement in 50% of patients undergoing surgical incision.

Mu receptor. The mu receptor is one of five opioid receptors associated with respiratory depression and narcotic addiction.

Myelin. Myelin is an insulating lipid layer that forms a sheath around certain nerve fibers which increases the rate of nerve impulse conduction.

Neospinothalamic system. The neospinothalamic system refers to one of the ascending pain pathways within the spinal cord that carries fast pain sensations of A-delta fibers.

Nociceptor. Nociceptors are receptors which detect painful stimuli.

Norepinephrine. Norepinephrine is a catecholamine neurotransmitter located in and released from the adrenal medulla and the sympathetic postganglionic nerve endings. Norepinephrine is also released in many other regions within the CNS.

Paleospinothalamic system. The paleospinothalamic system refers to one of the ascending pain pathways within the spinal cord that carries slow pain sensations of C-fibers.

Parasympathetic. The parasympathetic nervous system is that portion of the autonomic nervous system that originates from the cervical and sacral regions of the spinal cord, and is responsible for physiologic stability and energy conservation.

Periaqueductal grey matter. The periaqueductal grey matter is that portion of the midbrain with which the spinothalamic tract communicates.

Placebo. A placebo is an inactive substance resembling medication that may be given during an experiment or used for its psychologic effect.

Postganglion. The postganglion refers to neurons that lie distal to a ganglion and directly connect to the organ system it affects.

Prohormone. A prohormone is a protein molecule precursor of a hormone.

Proprioception. Proprioception refers to perception of movement associated with the sensation of a change in body position, such as in the extremities.

Prostaglandin. A lipid soluble protein derived from arachidonic acid, prostaglandins are associated with the inflammatory response and mediators of pain.

Reticular formation. The reticular formation is that portion of the brain stem which contains most of the vital reflex circuitry that controls respirations, cardiovascular function, swallowing, vomiting, and others.

Somatosensory. The term somatosensory pertains to body sensation.

Spinomesencephalic tract. The spinomesencephalic tract is one of several ascending pain pathways within the spinal cord.

Spinoreticular tract. The spinoreticular tract is a major ascending pain pathway, and is one of several pathways within the spinal cord.

Spinothalamic tract. The spinothalamic tract is another major ascending pain pathway, and is one of several pathways within the spinal cord.

Stereospecific. The term stereospecific pertains to enzymes that interact only with compounds of a specific structure.

Synapse. A synapse is the junction between nerve cells and may be either electrical or chemical. An electrical

synapse consists of a gap junction that permits direct transmission of ions. A chemical synapse prevents direct transmission of ions.

Sympathetic. The term sympathetic refers to that portion of the autonomic nervous system that originates from the thoracic and lumbar regions of the spinal cord and is responsible for adaptation to environment and response to stress.

Thalamus. The thalamus is an area within the brain that receives all types of sensory information.

Tourniquet. A tourniquet is a device used to prevent bleeding in an extremity by compression of blood vessels.

Trophtropic. The term trophtropic pertains to the parasympathetic nervous system which functions in the process of nourishment and conservation of energy (trophos = nourishment; tropic = releasing).

Vagal. The term vagal pertains to the vagus nerve and its subsequent parasympathetic response.

Ventrolateral funiculus. The ventrolateral funiculus is a collection of ascending pain pathways consisting of the spinoreticular tract, spinothalamic tract, and the spinomesencephalic tract.

Conceptual Framework

The occurrence of tourniquet pain or tourniquet-induced hypertension and tachycardia arises from noxious stimuli

produced by prolonged tourniquet inflation. The physiologic response is widespread and is propagated by peripheral nerve receptors that are linked to the central nervous system. Understanding the nature of the autonomic response requires a review of the nervous system. Insight as to why pharmacological agents used in general anesthesia alter this noxious response is also important.

Autonomic Nervous System

The peripheral and central nervous systems both have an involuntary component. The involuntary component of the peripheral nervous system is known as the autonomic nervous system (ANS). The ANS innervates smooth muscle, glands of visceral organs, and the heart. The function of the ANS is to maintain physiologic stability and allow adaptation to the outside environment. This function is largely independent of conscious thought. Thus, the process of adaptation is *autonomic*, not *automatic*. If the environmental change is acute, the ANS permits a rapid physiologic response. Consequently, the ANS is usually associated with an efferent neuron response and is considered a motor system. Some researchers believe that the afferent sensory component should also be included in the ANS component (Kapit & Elson, 1977; West, 1992).

Unlike the skeletal motor system which has a one-fiber pathway originating from the spinal cord to muscle, the ANS

has a two-fiber pathway leading to its destination. The first neuron fiber of the ANS arises within the CNS and is referred to as preganglionic. The axon of the first preganglionic neuron fiber travels peripherally to synapse with a second postganglionic neuron. The axon of the second postganglionic neuron then proceeds to its effector organ. In contrast to ANS motor neurons, sensory neurons that emerge from ANS innervated organs are structurally and functionally similar to somatic sensory neurons. Information is conflicting as to whether sensory neurons within the visceral structures are actually part of the ANS. Some researchers consider only the motor component and its effects as part of the ANS. Studies have shown that visceral afferent sensory neurons are the first link in the reflex arc of the ANS, whether transmitting visceral discomfort or changes in vascular perfusion. Most efferent motor neurons within the ANS are paralleled by visceral afferent sensory neurons (Lawson, 1992; West, 1993).

Since physiologic stability and adaptation are required for survival, the ANS is divided into two major systems: the parasympathetic (craniosacral) and sympathetic (thoracolumbar) nervous systems (Guyton, 1987). The parasympathetic nervous system (PNS) is trophtropic and primarily cholinergic in function. It contributes to maintenance and restoration of energy. Consequently, the PNS aids in meal digestion and reduction in heart rate and

respiratory rate. The cholinergic function of the PNS arises from postganglionic fibers that secrete acetylcholine at the nerve terminal endings. In contrast, the sympathetic nervous system (SNS) is ergotropic and performs an adrenergic function. It allows for adaptation to the environment and is associated with a "fight or flight" response that occurs during stressful situations (West, 1992). The SNS adrenergic function arises from the release of norepinephrine by a vast majority of postganglionic sympathethic nerve terminal fibers. A few sympathetic nerve terminals however are also known to secrete acetylcholine. A schematic diagram of the peripheral ANS is illustrated in figure 1.

Autonomic nervous system activation occurs mainly from regions located in the spinal cord, brain stem, and hypothalamus. The limbic system can also influence autonomic control by sending signals to the lower brain (Guyton, 1987). It is in the peripheral sensory receptors however that autonomic control begins. Upon stimulation of the peripheral sensory receptors, information is transmitted through afferent nerve fibers to receptors located in the spinal cord, brain, or hypothalamus. A feedback response occurs through the efferent nerve fibers causing a desired effect. In this manner, autoregulation of the peripheral organs and tissues occurs (Guyton, 1987).

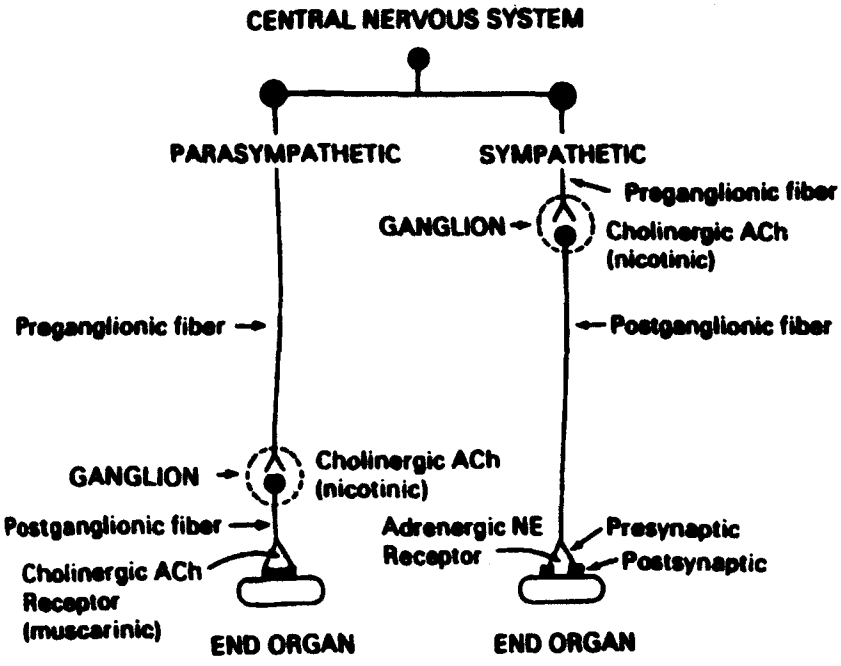
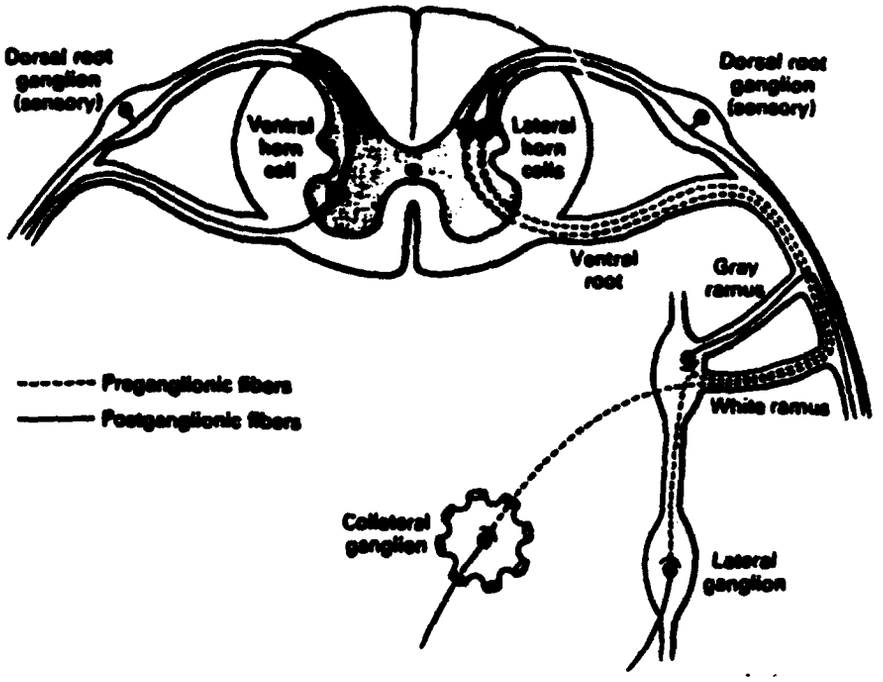


Figure 1. The Peripheral Autonomic Nervous System. Note. From Stoelting and Miller, 1989, Basics of Anesthesia, p. 26.

Sympathetic nervous system. Preganglionic nerve fibers of the SNS emerge from the first thoracic through the second or third lumbar vertebral levels. Each cell body from these nerve fibers originates in the interomedial lateral gray column of the spinal cord. Each has a short axon that travels through the anterior root of the spinal cord into a

spinal nerve. After a few centimeters, the preganglionic fiber leaves the spinal nerve and enters a ganglion of the sympathetic chain (see Figure 2). The preganglionic fiber



Anatomy of a sympathetic nervous system nerve. Preganglionic fibers pass through the white ramus to a paravertebral ganglia where they may synapse, course up the sympathetic chain to synapse at another level, or exit the chain without synapsing to pass to an outlying collateral ganglion.

Figure 2. Anatomy of a Sympathetic Nervous System Nerve. Note. From Stoelting, 1991, Pharmacology and Physiology in Anesthetic Practice, p. 647.

can then follow one of three courses: (a) synapse with the postganglionic fiber in the ganglia at the level that it exits; (b) pass through the sympathetic chain and synapse with a ganglia caudal or cephalad to its level of entry; or (c) exit the sympathetic chain to synapse with an outlying, unpaired SNS collateral ganglion. One exception is the adrenal medulla in which presynaptic fibers pass through the sympathetic chain without synapsing to a ganglion (Lawson, 1992; West, 1992). Embryonically, the tissue of the adrenal medulla originates from neuronal ectoderm and is analogous to neural tissue in the postganglion chain (Guyton, 1987). Cell bodies within the sympathetic chain are postganglionic and give rise to long axons. These axons terminate on designated organs to produce specific effects as depicted in figure 3.

Preganglionic sympathetic neurons affect a larger portion of postganglionic neurons at synapses. The ratio of preganglionic to postganglionic neurons can vary, but is usually 20:1. Consequently, a small number of activated preganglionic neurons can culminate into an immediate, widespread physiologic response. This response prepares the body to react against a threat and can be further augmented by hormonal release of epinephrine from the adrenal medulla (Lawson, 1992).

Research has shown that adrenergic receptors within the SNS consist of two types, alpha and beta. The alpha

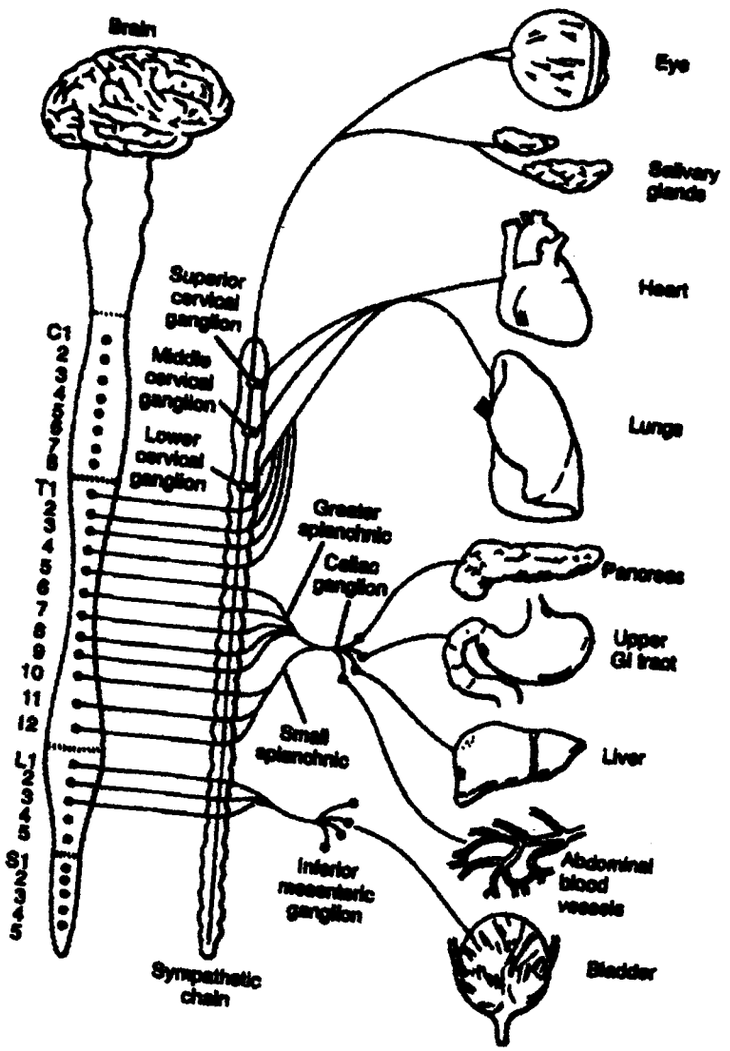


Figure 3. The Sympathetic Nervous System.

Note. From Morgan and Mikhail, 1992, Clinical Anesthesiology, p. 161.

adrenergic receptors are activated by norepinephrine, and are further subdivided into two subtypes, alpha-1 and alpha-2. Alpha-1 receptors are located on the postsynaptic target cells of smooth muscles of the peripheral vasculature and intestinal mucosa. The activation of these postsynaptic receptors causes constriction in vessels of capacitance and re istance, and intestinal tract relaxation. In contrast, the presynaptic alpha-2 receptors serve as a negative feedback mechanism and are known to inhibit release of norepinephrine. Postsynaptic alpha-2 receptors cause platelet aggregation and hyperpolarization of membranes in the CNS. Other alpha-2 receptors are located in cholinergic pathways where they modulate parasympathetic activity (Lawson,1992; Rhoades & Pflanzer, 1992).

Beta receptors are subdivided into beta-1 and beta-2 subtypes. Beta-1 receptors are located chiefly within the myocardium, sinoatrial node, ventricular conduction system, and adipose tissue. Beta-1 receptors, when stimulated, cause the heart to contract with increased force and rate and are equally affected by norepinephrine and epinephrine. In contrast, beta-2 receptors are stimulated by epinephrine, not norepinephrine, and induce vasodilation and bronchial relaxation of vascular smooth muscle within the skin, muscle, mesentery, and bronchial tree (Lawson, 1992; Rhoades & Pflanzer, 1992).

Nerve fiber classifications. Three main types of motor and sensory fibers have been classified. This classification is based upon nerve diameter size and myelination. Nerve fibers have been identified as either group A-, B-, or C-fibers by Erlanger and Gasser (1937) who studied mixed nerve trunk action potentials using a cathode ray oscillograph. Myelinated fibers were classified as either group A- or B-, in contrast to the unmyelinated group C-fibers. In general, group A-fibers have larger diameters. Faster conduction velocities are also associated with fibers that are larger and myelinated (see Table 1). Typically, group A-fibers perform a proprioceptive or somatic motor function. Pain sensation and autonomic function are common to the smaller nerve fibers such as the C-group or A-delta fibers (Guyton, 1987; West, 1991).

Mechanisms of pain. The occurrence of pain manifests by mechanisms that are numerous and complex. First, pain receptors receive noxious (harmful) stimuli from the periphery and transmit this information to higher neural centers. As the information is received, it is integrated and modulated within the thalamus and cortex. A subjective reaction to noxious stimuli is the final mechanism of this pathway. Receptors that receive and project painful stimuli, known as nociceptive receptors, are widely distributed throughout the skin and internal body organs (Curtis, 1986). Prior to cortical perception, impulses

Table 1

Classification of axons in mammalian peripheral nerve

Fiber class	Subclass	Diameter (μ)	Myelin	Conduction velocity (m/sec)	Location	Function
A	α	6-22	+	30-120	Efferent to muscles	Motor
I	a	10-22	+	50-100	Afferent from muscle spindles	Sensorimotor
A	β	6-22	+	30-120	Afferent from cutaneous joints	Tactile, proprioception
A	γ	3-6	+	15-35	Efferent to muscle spindles	Muscle tone
A	δ	1-4	+	5-25	Afferent sensory nerves	Pain, temperature, touch
B		<3	+	3-15	Preganglionic autonomic	Various autonomic functions
C	sC	0.3-1.3	–	0.7-1.3	Postganglionic autonomic	Various autonomic functions
C	dC	0.4-1.2	–	0.1-2.0	Afferent sensory nerves	Pain, temperature

Note: From Principles and Practice of Anesthesiology (p. 1199) by M. C. Rodgers, J. H. Tinker, B. G. Covino, and D. E. Longnecker, 1993, St. Louis: Mosby Year Book. Copyright 1993 by Mosby-Year Book, Inc.

arising from these receptors are modified at several levels traveling the afferent sensory neural pathways. Modulation of nociceptive impulses may develop in the periphery or at any synaptic point along the pathway of pain transmission (Lubenow, McCarthy, & Ivankovich, 1992).

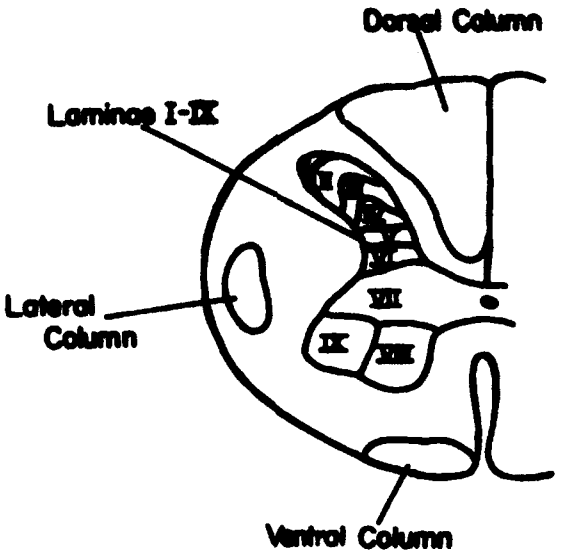
Peripheral modulation occurs through chemical mediation. These chemical mediators, when liberated, sensitize or excite the nociceptors and are known as algogenic mediators. Potassium and hydrogen ions, lactic

acid, serotonin, bradykinin, histamine, and prostaglandins are examples of algogenic mediators (Lubenow et al., 1992). Nociceptors are free nerve endings and may be associated with the myelinated A-delta (fast), or unmyelinated C-fibers (slow). These fibers account for the components of pain perception. The first pain that occurs with trauma is often localized, sharp, and immediate. This portion of the pain response is related to the A-delta fibers. The smaller C-fibers have a slower transmission rate and account for extremely unpleasant, dull, aching, burning, and diffuse pain. The C-fibers can summate pain impulses over time to cause even weak signals from initially tolerable discomfort to unbearable pain (Curtis, 1986; Stoelting, 1991).

Nociceptors encode information concerning the occurrence, intensity, duration, and location of noxious stimuli. Pain sensation is transmitted from pain receptor's bare afferent nerve endings by myelinated A-delta and unmyelinated C-fibers. These nociceptors are located throughout the superficial layers of the skin. Nociceptors can also be found on certain internal body structures including the periosteum, joint surfaces, skeletal muscle, and tooth pulp. Deep tissue structures are not richly innervated with pain receptors, although widespread damage may initiate an achy sensation through summation of pain impulses (Stoelting, 1991).

Pain receptors or nociceptors in the skin have been classified into three types. The mechanosensitive pain receptor is activated by means of mechanical stimulation and transmit pain impulses via the A-delta fibers. A second type of nociceptor is activated by mechanical and thermal stimulation. This type of pain receptor is referred as a mechanothermal receptor. A third nociceptor is classified as a polynodal pain receptor and can be activated by mechanical, thermal, and chemical stimuli. Consequently, the polynodal pain receptor responds to algogenic mediators. The polynodal receptor sends impulses by means of unmyelinated C-fibers (Stoelting, 1991).

Pain signals originate from nociceptors and transmit impulses along unmyelinated C-fibers or myelinated A-delta fibers. These afferent fibers enter the spinal cord at the dorsal nerve roots and synapse within the gray matter of the dorsal horn. Anatomically, the gray matter within the dorsal horn is divided into anterior, lateral, and dorsal tracts consisting of nine separate laminae (see Figure 4). The C-fibers synapse with cells located in laminae II and III of the spinal cord. Cells located in laminae I and V are synapsed with A-delta fibers. Pain impulses, once processed in the dorsal horn, may travel one of several ascending pathways along the ventrolateral quadrant of the spinal cord. Collectively, these ascending pathways are



Schematic diagram of a cross-section of the spinal cord depicting anatomic laminae I to IX of the spinal cord gray matter and the ascending dorsal, lateral, and ventral sensory columns of the spinal cord white matter.

Figure 4. Schematic Diagram of a Spinal Cord Cross-Section. Note. From Stoelting, 1991, Pharmacology and Physiology in Anesthesia Practice, p. 618.

known as the ventrolateral funiculus (VLF). Pain fibers in the ventrolateral quadrant cross over to the opposite side of the spinal cord, although some do not cross over until reaching the brain. Consequently, most pain signals ascend from the contralateral dorsal horn. Ascending pathways of

the VLF include the spinoreticular tract, spinothalamic tract, and the spinomesencephalic tract. Tracts located in the dorsum of the VLF are associated with touch and proprioception, but not pain. Areas within the medial portion of the VLF known as the paleospinothalamic system transmit impulses from slow-conducting C-fibers. Tracts within the paleospinothalamic system project to the reticular formation, periaqueductal grey matter, hypothalamus, medial thalamus, and limbic system (see Figure 5). Reflexes associated with ventilation, circulation, endocrine function, and motivational-affect responses are elicited through the paleospinothalamic system. The fast-conducting A-delta fibers are conducted through the lateral portion of the VLF and are known as the neospinothalamic system. The neospinothalamic system projects to the lateral thalamus and interconnects to the somatosensory cortex of the brain. This system permits analysis of painful stimuli according to the location and type of pain (Phillips, 1991; Porth, 1988; Stoelting, 1991).

The phenomenon of pain modulation was first theorized in 1965 by Melzak and Wall. The authors postulated a neural-gating mechanism in the dorsal horn of the spinal cord. This mechanism controls peripheral nerve flow impulses to the spinal cord that projects to the brain (Melzack, 1988). In this manner, pain is modulated at the segmental spinal level prior to pain perception. The

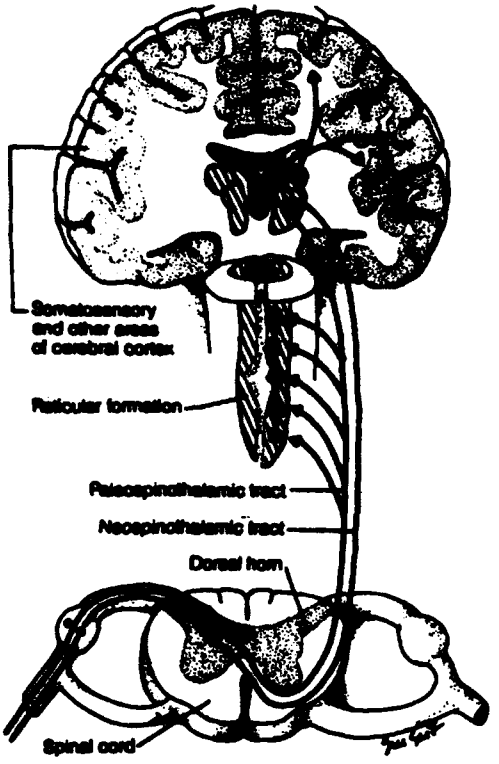


Figure 5. The Paleospinothalamic and Neospinothalamic Tracts.

Note. From Porth, 1988, Pathophysiology Concepts of Altered States (2nd Ed.), p. 872.

segmental spinal level gate is formed by a network of transmitting t-cells and internuncial neurons that can inhibit t-cell transmission. The internuncial neurons are

activated by the larger diameter and faster propagating fibers that transmit tactile stimuli such as touch. Consequently, pain intensity is temporarily reduced with active tactile stimulation. This causes the larger tactile fibers to fire and block transmission of the smaller myelinated and unmyelinated pain-transmitting fibers. Current research shows that the exact aspects of neural modulation have a much greater complexity than was first proposed by the gate-theory (Curtis, 1986). The concept of input modulation described by the gate-theory however remains valid despite much controversy (Melzack, 1988).

Tourniquet Pain

Tourniquet pain usually occurs after approximately 45 to 60 minutes of tourniquet inflation. The precise reason for its occurrence has not been identified, yet a variety of theories exist. Both Cole (1952), and Egbert and Deas (1962) theorize that tourniquet pain originates in larger nerve fibers that differ from those fibers carrying other nociceptive stimuli. Conversely, de Jong (1984) concludes that small A-delta and C-fibers may produce impulses cephalad to the sensory block. It has also been conjectured that C-fibers return to normal function sooner than A-fibers as the concentration of local anesthetic diminishes (Gissen, Covino, & Gregus, 1980). Kaufman and Walts (1982) hypothesize that tourniquet compression causes

conduction loss in the larger A-delta fibers prior to the smaller unmyelinated C-fibers. The inhibition of large myelinated fibers allows for unopposed firing of C-fibers. Consequently, prolonged tourniquet compression causes a diffuse, burning, and aching pain associated with slow pain fibers.

Prostaglandins

Prolonged tourniquet pressure may cause the release of prostaglandins. Prostaglandins are local chemical mediators with diverse effects involved in inflammation and pain-modulation. Prostaglandins are formed from the conversion of arachidonic acid utilizing the enzyme cyclooxygenase (see Figure 6). Conceivably, tourniquet pain could be reduced by limiting the amount of prostaglandin production. Ketorolac tromethamine inhibits cyclooxygenase thus preventing the conversion of arachidonic acid to prostaglandins. Since centrally-acting narcotics are not very effective against reducing tourniquet pain, perhaps a peripherally-acting agent would be. Ketorolac tromethamine is a peripherally-acting drug capable of inhibiting prostaglandins. In contrast to ketorolac tromethamine, narcotics carry the intrinsic risk of respiratory depression, cardiovascular instability, and addiction. Consequently, tourniquet pain requiring higher doses of narcotics may limit their use (Brown, Moodie, Wild, & Bynum, 1990).

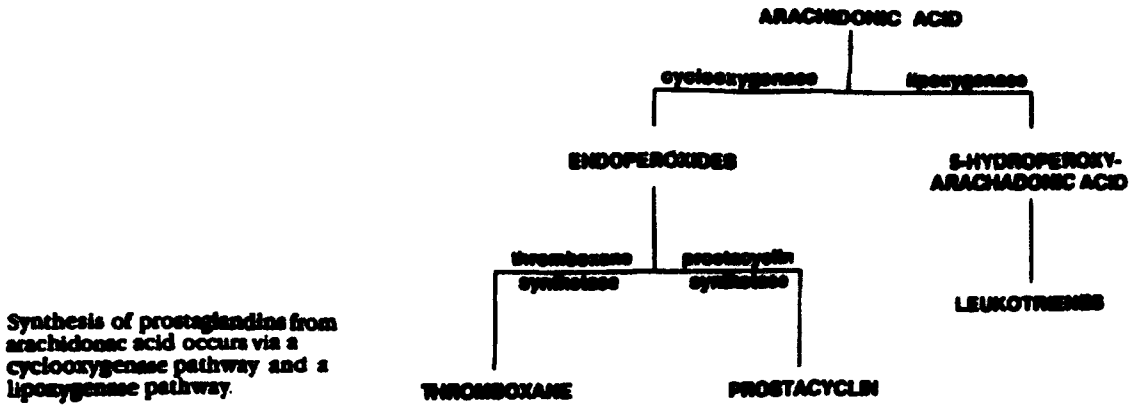


Figure 6. Synthesis of Prostaglandins.

Note. From Stoelting, 1991, Pharmacology and Physiology in Anesthetic Practice, (2nd ed.), p. 385.

Opioids

The pharmacologic action of opioids is centrally mediated. Opioids are stereospecific agonists acting at presynaptic and postsynaptic receptor sites within the CNS. Normally these receptors are activated by endorphins, the body's own endogenous pain-suppressors. Endorphins are manufactured in the anterior pituitary gland as a prohormone. The hydrolysis of a prohormone gives rise to an endorphin. Opioid receptors are located in the brain's

periaqueductal grey matter, amygdala, corpus striatum, substantia gelatinosa, and within the substantia gelatinosa of the spinal cord. Both opioids and endorphin polypeptides inhibit excitatory neurotransmitters of those terminal nerve tracts carrying nociceptive stimuli (Stoelting, 1991).

Ketorolac Tromethamine

In contrast to opioid action, ketorolac tromethamine is a nonsteroidal, anti-inflammatory drug (NSAID) that does not have CNS activity. It is a potent analgesic with less anti-inflammatory activity than other NSAIDs. Ketorolac tromethamine's action is based peripherally in the body by inhibition of the prostaglandin synthesis-mediated cyclooxygenase. While ketorolac tromethamine may have some sedative effects in certain individuals, it does not have opioid side effects of euphoria and respiratory depression. It is believed that two opioid receptor sites, mu and kappa, are responsible for these side effects. Since ketorolac tromethamine does not bind to opioid receptors, its administration lacks the addictive or drug withdrawal effects often associated with opioid administration (Bachhuber, 1992). Moreover, Brown et al. (1990) states that ketorolac tromethamine can be administered intravenously at a comparably higher and safer dose than can morphine sulfate. A dose of 10 mg of ketorolac

tromethamine, intramuscularly (IM), has been shown to be as effective as 12 mg of morphine sulfate, IM (Yee, Koshiver, Allbon, & Colin, 1986). Studies by Camu, Overberge, Bullingham, and Lloyd (1990), and Kenny, McArdle, and Aitken (1990) reveal ketorolac tromethamine has little to no cardiovascular or respiratory depression. The onset of ketorolac tromethamine's action occurs within 30 minutes of intramuscular injection, and peak effect occurs 2 to 3 hours after administration (Johansson, Josefsson, Malstam, Lindstrand, & Stenstroem, 1989). Excretion of ketorolac tromethamine occurs primarily through the urine (92%) as unchanged ketorolac tromethamine, ketorolac glucuronide, or p-hydroxyketorolac (Jung, Mroszczak, & Bynum, 1988).

General Anesthesia

General anesthesia is a reversible process that modulates neurologic function at synaptic communications. This reversible disruption in neurologic function leads to losses in sensory perception, reflex reaction to pain, awareness of immediate events, and memory of those events. Typical attributes of general anesthesia include analgesia, amnesia, skeletal muscle relaxation, and unconsciousness. Scientific opinions are conflicting regarding the site of action of general anesthetics within the CNS. One theory considers consciousness to be in a discrete CNS location. Another theory views consciousness as an integration of many

regions in the brain working in unison. On a cellular level, an anesthetic agent's most likely site of action is the neural synapse. The manner in which this synaptic disruption occurs, owing to the vast complexity and neurologic interdependence within the CNS, remains unclear (Alifimoff & Miller, 1993; Ritcher, 1992).

The purpose of general anesthesia is to maintain an adequate level of neurological depression for the patient during surgical stimulation. As surgical stimulation changes, anesthetic depth may be altered by changing the concentration of an immediate acting, easily controllable inhalation agent. Anticipating periods of minimal and maximal surgical stimulation allows for proper maintenance of volatile gas concentrations. Several volatile agents, each varying in potency, can be used.

Knowledge of the pharmacodynamics and pharmacokinetics of various volatile agents is essential to administer the proper dose of each inhaled anesthetic. In 1965, Eger, Saidman, and Brandsteter developed a measure to estimate various inhalation agent potencies. The minimal alveolar concentration (MAC) standardizes the concentration of each inhaled gas to a depth of anesthesia that would prevent a response to a standard surgical incision in 50% of patients. The MAC of an inhalation agent is established experimentally by maintaining a stable alveolar partial pressure for approximately 15 minutes. This permits time for the

volatile gas to achieve equilibrium between arterial blood and brain tissue. Whereupon a painful stimulus is initiated, any movement occurring in response to the stimulus is noted. These results are plotted against alveolar or end-tidal anesthetic concentration and then interpolated at 50% to determine MAC. The advantage of determining MAC is the establishment of relative constancy of measure within a species. This allows predictable administration of an agent as well as a direct estimation of anesthetic depth from measuring expired gas concentrations. Furthermore, the potency of each inhalation agent as well as those used in combination with other agents can be compared using MAC. One-half MAC of two agents used in combination is equivalent to one MAC of either agent used alone. For example, the application of MAC can be demonstrated with the use of nitrous oxide and isoflurane. Normally the MAC of isoflurane is 1.15% in an oxygen mixture, but can be reduced to 0.5% in a 70% nitrous oxide: 30% oxygen mixture (Longnecker & Miller, 1993; Stevens & Kingston, 1992).

The desired effect during anesthetic induction depends upon the inhalational agent reaching a sufficient partial pressure in the brain. Rapid uptake occurs with agents such as isoflurane which has low blood and tissue solubility. Isoflurane passes from higher inspired gradients within the lung to lower gradients in the blood, then to the body

tissues. As long as a gradient exists, uptake and distribution continues in this stepwise fashion. Pharmacodynamically, the induction of anesthesia is complete when gas tension of the inhalation agent in the lung reaches equilibrium in all tissues (Stevens & Kingston, 1992).

General anesthesia effects blood pressure by decreasing receptor sensitivity within the autonomic nervous system. A decrease in baroreceptor sensitivity occurs with all inhalational agents in a dose dependent manner. Baroreceptors located in the carotid sinus and aortic arch provide the peripheral sensory component for detecting blood pressure changes. Central mediation of blood pressure changes occurs within the areas of the hypothalamus and brain stem. These peripheral and central baroreceptors respond to decreases in blood pressure by enhancing sympathetic tone and diminishing vagal tone. This results in increases in heart rate and enhancement of cardiac contractility to elevate blood pressure. Conversely, hypertension is modified through increased vagal tone and suppressed sympathetic tone. All volatile inhalational agents are known to variably depress this reflex at several sites in the body. These sites are the peripheral baroreceptors, sympathetic ganglia, and end-organ response to autonomic stimulation (Assef, 1991; Morgan & Mikhail, 1992).

Systemic vascular resistance (SVR) decreases during anesthetic induction using isoflurane. The cardiovascular response shows little change in cardiac output, yet blood pressure drops secondary to decreased SVR (Longnecker & Miller, 1993). Noxious stimulation such as tourniquet pain diminishes this drop in blood pressure. Sympathetic response to prolonged tourniquet pressure results in an increased heart rate and blood pressure. Therefore, attenuating this sympathetic response may require an increased concentration of isoflurane.

Summary

The autonomic nervous system is largely an involuntary component of the peripheral nervous system. The parasympathetic nervous system and sympathetic nervous system are two components within the ANS. The PNS has a cholinergic function and provides restoration and maintenance of energy (trophtropic). The PNS arises from the craniosacral portion of the spinal cord. In contrast, the SNS expends energy (ergotropic) and is adrenergic in function. The SNS provides for adaptation to the environment and reaction to danger as seen in a "fight or flight" response. A larger number of postsynaptic sympathetic neurons are affected by a smaller number of preganglionic neurons at the point of synapse. Because of this ratio, a "fight or flight" response quickly occurs.

The SNS has two receptor types referred to as alpha and beta. These receptors can be further differentiated into subtypes alpha-1, alpha-2, beta-1, and beta-2. Alpha-1 receptors are located in smooth muscles of the peripheral vasculature and intestinal mucosa, and cause arterial vasoconstriction and intestinal tract relaxation. Alpha-2 receptors provide a feedback mechanism and inhibit the release of norepinephrine. Alpha-2 receptors can also be associated with platelet aggregation, membrane hyperpolarization within the CNS, and modulation of parasympathetic activity. Beta-1 receptors are located within the heart and adipose tissue. Stimulation of these receptors causes the myocardium to increase its force and rate of contraction. Norepinephrine and epinephrine equally affect beta-1 receptors. Beta-2 receptors respond to epinephrine and not norepinephrine. Beta-2 receptor stimulation causes bronchodilation of the lungs and vascular vasodilation of smooth muscles in the skin, muscle, and mesenteries.

Motor and sensory nerve fibers have three classifications according to diameter size and myelination. Those classified A- and B-fibers are myelinated, in contrast to the unmyelinated C-fibers. The group A-fibers generally have larger diameters and are associated with faster conduction velocities. Pain sensation is associated with the small myelinated A-delta and unmyelinated C-fibers.

Mechanisms of pain transmission are numerous and complex. Modulation of pain as part of this mechanism can occur anywhere along one of the neural pathways from the periphery to the CNS. Noxious stimuli is perceived by sensory receptors called nociceptors and this information is transmitted to higher neural centers. Impulses conducted from a nociceptor may be associated with slow, unmyelinated C-fibers, or fast, myelinated A-delta fibers. When tissue injury occurs, impulses from A-delta fibers produce an immediate, sharp, and localized pain. This is followed by an extremely unpleasant, dull, achy, burning, diffuse pain associated with C-fibers. A neural gating mechanism for pain modulation has been proposed which shows that activation of the larger myelinated fibers blocks transmission of the smaller pain transmitting fibers. Furthermore, nociceptors can be chemically mediated by various substances.

Nociceptors are located in superficial layers of skin and internal body structures. Deep structures are not richly innervated with pain receptors. Information concerning the occurrence, intensity, duration, and location of noxious stimuli are encoded by nociceptors. These nociceptors are classified into three types: mechanosensitive, mechanothermal, and polynodal. Nociceptive impulses are transmitted by means of A-delta or C-fibers, and enter the spinal cord at the dorsal nerve

roots. The nine laminae within the spinal cord are divided into anterior, lateral, and dorsal tracts. Pain impulses travel along one of several acending pathways collectively called the ventrolateral funiculus. The ascending pathways of the ventrolateral funiculus are composed of the spinoreticular, spinothalamic, and spinomesencephalic tracts. The C-fibers are associated with medial tracts within the ventrolateral funiculus, and are part of the paleospinothalamic system. Impulses traveling the paleospinothalamic system elicit reflexes associated with ventilation, circulation, endocrine function, and motivational-affect response. The lateral tracts of the ventrolateral funiculus, known as the neospinothalamic system, conduct impulses from the A-delta fibers. Impulses traveling the neospinothalamic system elicit reflexes that permit painful stimuli to be analyzed according to location and type of pain.

The occurrence of tourniquet pain is usually elicited after 45 to 60 minutes of tourniquet inflation. Most theories link tourniquet pain to C-fibers since prolonged tourniquet application causes a diffuse, burning, and aching pain in the awake patient. Release of prostaglandins with prolonged tourniquet application and inflation is a reasonable explanation for tourniquet pain. Prostaglandins are a chemical pain-mediator that sensitize or excite nociceptors into firing. Prostaglandins increase the

stimulus associated with slow impulse C-fibers. Normally, larger myelinated fibers modulate impulses from C-fiber nociceptors. It is conjectured that during tourniquet compression, the larger myelinated fibers remain inhibited while normal functioning of the now unopposed C-fibers returns sooner. Therefore, if prostaglandin release is associated with tourniquet pain, reduction of prostaglandins should reduce adverse sequelae or manifestations of tourniquet pain.

Ketorolac tromethamine is a nonsteroidal, anti-inflammatory drug that inhibits prostaglandin production. Administration of ketorolac tromethamine prior to tourniquet inflation may reduce tourniquet pain without the adverse effects associated with opioids. Studies have shown that the efficacy of ketorolac tromethamine 10 mg, IM, is similar to morphine sulfate 12 mg, IM (Brown, Moodie, Wild, & Bynum, 1990; Yee, Koshiver, Alllbon, & Brown, 1986). Ketorolac tromethamine's onset of action occurs within 30 minutes following its administration, and is primarily excreted in the urine.

General anesthesia is a reversible disruption in neurologic function. The purpose of general anesthesia is to maintain an adequate neurologic depression in response to surgical stimulation. Knowledge of volatile anesthetics and their relative potencies can assist the anesthetist in maintaining an adequate depth of neurologic depression for

the patient during surgery. The minimal alveolar concentration establishes a standard to which various inhalation agents can be compared. Furthermore, MAC values of particular agents are additive so that one-half MAC of two different agents equal one MAC when both agents are combined. The MAC value permits predictable physiologic results and estimated depth of anesthesia when using one or more inhalational agents. The desired effect of induction, when administering anesthesia, depends upon sufficient agent reaching the brain. Establishment of anesthesia is complete when the gas tension of the inhalation agent reaches equilibrium between the lung and other tissues. General anesthesia affects blood pressure by decreasing baroreceptor sensitivity. Baroreceptors modify blood pressure by enhancing sympathetic tone and diminishing vagal tone if blood pressure is low, and diminishing sympathetic tone and enhancing vagal tone if blood pressure is elevated. All volatile inhalational agents, to varying degrees, depress the baroreceptive reflex. While volatile agents such as isoflurane decrease heart rate and blood pressure, noxious stimuli can alter this response. Therefore, tourniquet pain may require higher MAC concentrations to attenuate the sympathetic response of increased blood pressure and heart rate.

Review of Literature

Tourniquet-Induced Hypertension and Pain

Crews, Hilgenhurst et al. (1991) investigated 3 factors of tourniquet pain related to duration of tourniquet inflation. These factors included tourniquet width, tourniquet inflation pressure, and right or left extremity tourniquet application. The upper extremities of twelve (N = 12) healthy, unmedicated volunteers were used for this study. The average tourniquet inflation duration was 34 +/- 13 minutes. A verbal pain score (VPS) was utilized to quantitate pain intensity. A score of "0" indicated no pain; a score of "10" represented severe pain. No significant differences were noted in heart rates or blood pressures in the control or study groups. The results of the study revealed no correlation of the 3 factors to either pain intensity or tolerance to tourniquet inflation.

Crews and Sehlhorst (1991) designed a study to monitor circulatory and stress response to tourniquet pain in 8 African Green monkeys. The monkeys were anesthetized with an intramuscular injection of 10 mg/kg ketamine, and heart rates and blood pressures were monitored every 5 minutes. Pain related to tourniquet pressure remains poorly understood and is characterized by a severe, dull, aching

sensation at the tourniquet site or distal to the site. Results of this study demonstrated increases in heart rates and blood pressures in the anesthetized monkeys after 30 to 45 minutes of tourniquet inflation. The authors postulated that the circulatory response was mediated by a neurohumoral response to tourniquet pressure. Serum cortisol and plasma norepinephrine levels correlated to a progressive increase in heart rate and blood pressure. The authors concluded that animal models are appropriate for further research to identify tourniquet pain etiology.

Another study by Egbert and Deas (1962) evaluated patients undergoing orthopedic surgery utilizing a pneumatic tourniquet who also received subarachnoid anesthesia. All patients (N = 106) received a preoperative, intravenous injection of methoxamine, 10 mg, prior to initiation of subarachnoid anesthesia. The subjects were randomly assigned to 1 of 2 groups. Group one (n = 55) received a subarachnoid injection of tetracaine, 12 mg, and group two (n = 51) received a subarachnoid injection of tetracaine, 16 mg. Dermatome levels were tested for motor loss by diminished leg movement, and for sensory loss by reaction to pinprick. Once an acceptable subarachnoid anesthetic block was established, a pneumatic tourniquet was placed over a Webril pad on the patient's affected extremity and inflated to 550 mmHg. Results of this study concluded that 35 subjects in group one (63.6%), and 17 subjects in group two

(33.3%) experienced pain in spite of subarachnoid anesthesia. Consequently, those subjects receiving the lesser dose of subarachnoid tetracaine were at greater risk than those receiving the larger dose for experiencing pneumatic tourniquet pain.

Hagenouw, Bridenbaugh, Van Egmond, and Stuebing (1986) examined the effects of tourniquet inflation pressure of 300 or 400 mmHg, tourniquet width of 5 or 7 cm, and methods of exsanguination using either gravity or an Esmarch bandage. The trial included 11 healthy, unpremedicated, adult volunteers. Results of this study revealed no difference between tourniquet pressures of 300 or 400 mmHg to onset of pain, although the volunteers could subjectively tell the difference between the two tourniquet pressures. Circulatory occlusion was complete at 350 mmHg inflation using the 7 cm width tourniquet. The 5 cm width tourniquet caused less discomfort but required higher occlusion pressures. Higher occlusion pressures were associated with compression trauma to tissues and nerves. The volunteers in the study demonstrated that an inflated tourniquet could be tolerated for a mean of 31 minutes. Spinal or epidural anesthesia, if utilized, extends tourniquet pain tolerance to 60 to 90 minutes. The authors noted that with tourniquet inflation times greater than 1 hour, an increased incidence of hypertension occurred.

Tourniquet pain is unlikely to be related to vascular ischemia since there are no reports of pain phenomenon occurring in patients undergoing clamping of an artery, the aorta, or with major arterial cross-clamping while receiving subarachnoid anesthesia. Tourniquet pain may occur anywhere along the extremity with tourniquet application. Hagenouw et al. (1986) also conclude that additional sources of tourniquet pain result from direct pressure on the nerve trunk or from sensory innervation within the vascular bed.

Prompted by the death of a hypertensive patient who had undergone orthopedic surgery with an applied pneumatic tourniquet, Valli, Rosenburg, Kytti, and Nurminen (1987) completed a retrospective study on 699 male patients undergoing similar orthopedic surgery. The study required a pneumatic tourniquet application for at least 1 hour. General (n = 240) and spinal (n = 335) anesthetics were used in this study. Other anesthetic methods utilized intravenous regional anesthesia (n = 59), brachial plexus blockade (n = 40), and a combination of regional with general anesthesia (n = 25). Hypertension was defined as a 30% increase in systolic blood pressure, diastolic blood pressure, or both from baseline values. Results demonstrated that patients receiving general anesthesia (18.1% of the subjects) had the highest occurrence of tourniquet-induced hypertension. Only a small percentage of subjects who received spinal anesthesia (2.7%) or brachial

plexus blockade (2.5%) developed hypertension. A 19% incidence of tourniquet-induced hypertension occurred in those subjects receiving intravenous regional anesthesia. Older patients, those undergoing longer operations, or those having tourniquet application to the lower limb had a higher frequency of tourniquet-induced hypertension. Conclusions of this study confirmed previous investigations that tourniquet-induced hypertension is more often associated with general anesthesia than with other methods of anesthesia.

The typical general anesthetic technique used in this study included nitrous oxide and opiates supplemented with enflurane or halothane. The authors found, as did Rocco, Concepcion, Desai, Dhingra, and Murray (1987), that hypertensive response associated with thigh tourniquet pressure does not occur in conjunction with tachycardia. Physiologically, the authors surmised progressive hypertension caused by tourniquet pressure was mediated by pain sensation via C-fibers. This response cannot be blocked by normal doses of opiates or volatile inhalation agents.

Kaufman and Walts (1982), in a retrospective study, reviewed 600 anesthetic records to determine the prevalence of tourniquet-induced hypertension and potential prognosticators for tourniquet pain development. One hundred subjects had no tourniquet applied and were used as

the control group. They were compared to 500 subjects who had procedures requiring the use of a tourniquet. Numerous variables were accounted for in this study, i.e., same group of surgeons, same operating room and monitors, same group of anesthetic caregivers. The patient's evaluation recorded general information, i.e., age, sex, race, and health condition. Hypertension was identified as systolic or diastolic blood pressures over 30% of baseline readings. Multivariate analysis was completed on all risk factors using logistic regression. The type of anesthesia administered, cardiac enlargement, and age were determined to be the only significant risk factors of tourniquet-induced hypertension. The overall frequency of tourniquet-induced hypertension approached 11%. The authors concluded that tourniquet pressure was the chief precipitating factor relating to detrimental effects of blood pressure variation.

In this study, intraoperative hypertension was not related to pre-existing hypertension, increased creatinine concentration, anemia, or treatment with antihypertensives, steroids, or diuretics. Variance in anesthesia did not cause hypertension to occur in the control group. Unlike the subjects with tourniquet application, hypertension related to light anesthesia occurred without latency in the control group. In some cases, the hypertensive response was corrected by deepening volatile anesthesia or by administering narcotics. Consequently, the frequency and

severity of tourniquet-induced hypertension could be underestimated in many patients.

The displacement of blood from the extremity to the central compartment occurred with tourniquet placement. Systolic blood pressure increased within 15 minutes of tourniquet inflation and averaged 18 mmHg above baseline values. The authors stated that the efficacy of various anesthetic agents resulted from blocking afferent C-fibers. Afferent C-fibers were previously inhibited by A-delta fibers prior to tourniquet inflation. Compression of myelinated A-delta fibers caused loss of nerve conduction sooner than "slow" C-fibers (Kaufman & Walts, 1982).

A study by Kojo and Pertovaara (1986) studied 5 subjects separated into 3 groups. A pneumatic tourniquet was placed on the upper arm of each subject. Cuff pressures of 200 and 300 millimeters of mercury (mmHg) were applied to all subjects in 2 groups. A third group had an inflated cuff pressure of 200 mmHg, but also combined submaximal exercise to quickly induce limb ischemia.

After application of the tourniquet and induction of limb ischemia, the authors studied cutaneous thermal sensations for hot and cold thresholds. The study examined whether heat-pain threshold occurred as a cool or warm sensation during tourniquet-induced ischemia. Thin myelinated A-delta fibers were associated with cool sensations, whereas C-fibers mediated warm sensations in

human skin. The study also determined if tourniquet-induced block of A-fibers was caused by ischemia or mechanical pressure.

Results of the study were consistent with previous studies in that cool sensations are mediated through thin myelinated A-delta fibers. After 15 minutes of cuff inflation, cool threshold sensations increased significantly in the ischemic arm. In contrast, the pain threshold to heat mediated by pressure and ischemic resistant C-fibers revealed no change. The authors concluded that the contact thermostimulator provided the clinician with a select method for testing nociceptive sensitivity of C-fibers by quantitative determinations of cutaneous heat-pain thresholds. Very hign rates of temperature change however activated A-delta fibers which were associated with the first intense pain sensation. Initial tourniquet pressure also caused warm thresholds to increase. This result was unexpected by the authors, and was tentatively explained as some kind of masking effect in the nervous system at higher neural levels.

Subjects in the study reported pricking sensations to cool or cold stimuli in the tourniquet-induced ischemic arm. The authors determined that these findings presented indirect support to the hypothesis that cold pain is mediated through C-fibers. Consequently, C-fibers provided cold pain as a possible neural substrate. Increasing the

work of an extremity by exercise with an inflated pneumatic tourniquet blocked A-delta fibers sooner and caused an earlier rise in cold-sensation threshold. The study lacked any conclusion concerning the relative importance of pressure and ischemia in tourniquet-induced block of cutaneous A-delta fibers. Neither did it provide suggestions for further research related to this topic. Lastly, the study group was quite small (Kojo & Pertovaara, 1986).

Rocco et al. (1987) completed a study that divided 30 patients into 3 equal groups receiving either spinal, epidural, or general anesthesia for lower extremity surgery requiring the use of a tourniquet. Laboratory analysis of plasma norepinephrine, epinephrine, cortisol, and glucose was obtained prior to induction of anesthesia, before tourniquet inflation, and 5 minutes after tourniquet deflation. The analysis results were then correlated to baseline blood pressure values. The blood pressure values in the general anesthesia group remained higher than blood pressure values in the spinal or epidural group until tourniquet deflation. Neither heart rate nor plasma levels of epinephrine changed significantly in any of the groups. Plasma norepinephrine levels rose in the general anesthesia group, yet there was no correlation to blood pressure fluctuation. The authors concluded that blood pressure increases seen with tourniquet occlusion in the general

anesthesia group did not appear to be related to an increased level of circulating catecholamines. Limitations of this study included a small sample size and little preliminary data, as acknowledged by the authors.

Valli and Rosenberg (1985) examined patients undergoing orthopedic surgery of the lower extremities using a tourniquet. Circulatory parameters were compared between patients receiving spinal, epidural, or general anesthesia. The authors assumed that regional anesthesia using a high spinal block could eliminate the hemodynamic effects of tourniquet pain. Subjects were comprised of 51 healthy ASA-I patients. The patients were assigned to 1 of 3 groups. Group one, receiving general anesthesia, consisted of 15 patients. Thiopentone was used as the induction agent, and suxamethonium was administered to facilitate endotracheal intubation. Maintenance of anesthesia was achieved with enflurane 0.8% to 1.5%, and nitrous oxide and oxygen mix of 70:30%. Group two received spinal anesthesia. An injection of 3 ml of plain 0.5% bupivacaine was administered into the subarachnoid space. The level of anesthesia was regularly assessed throughout surgery by serial pin pricks to the skin. Group three consisted of 20 patients receiving epidural anesthesia. A total dose of 20 ml of 0.5% bupivicaine was injected into the epidural space in incremental doses. The level of epidural anesthesia was confirmed in the same manner as in the spinal

anesthesia group. Mean analgesia dermatome ranges were determined to be at T-5 in both the spinal and epidural groups.

Results of the study demonstrated that 8 of 15 general anesthesia patients had blood pressure increases over 30% of their reference values. Only one patient receiving spinal anesthesia exhibited a transient rise in arterial blood pressure greater than 30%. However, two patients in this group felt pain, and an additional four patients felt pressure from the tourniquet. No patients in the epidural group had elevations in arterial blood pressure, but 11 of 15 patients required additional analgesia, sedation, or both for relief from pain or restlessness. The study revealed that tourniquet-induced hypertension occurred more readily in patients receiving general anesthesia than those receiving other forms of anesthesia.

This study was well planned and controlled for many variables. Unfortunately, no concluding statement concerning the study's findings was provided to the reader.

Ketorolac Tromethamine Compatibility with IV Fluids

The compatibility of ketorolac tromethamine in a wide variety of commonly used IV fluids was studied by Floy, Royko, and Fleitman (1990). Both physical and chemical compatibility were evaluated. Physical compatibility was estimated by visual analysis, particle counter, and pH

measurements. Chemical compatibility was determined by high-performance liquid chromatography. Absorption of ketorolac tromethamine within the administration set components and containers was also determined. The study analysis showed no degradation or absorption of ketorolac tromethamine within the containers or administration sets. Unfortunately, the authors did not recommend any type of safety profile for intravenous administration of ketorolac tromethamine.

Onset of Action with Ketorolac Tromethamine

Onset of analgesia following intramuscular injection of morphine sulfate 10 mg, ketorolac tromethamine 30 mg, or placebo was analyzed by Rice, Lloyd, Miller, Bullingham, and O'Sullivan (1991). The experimental design consisted of 85 patients in a double-blind, randomized, parallel group. Patients receiving a placebo functioned as the control group. The authors defined onset of analgesia when 25% of the patients achieved a 50% reduction in baseline pain intensity scores. Findings revealed ketorolac tromethamine has a significantly faster onset than the placebo, and no significant difference in effectiveness with morphine sulfate. No significant differences in the onset of analgesia were seen in patients receiving either placebo or morphine sulfate injections. Therefore, it is assumed that analgesic onset of morphine sulfate or ketorolac

tromethamine, IM, is similar in the context of postoperative pain relief. The authors concluded that more attention should be given to the speed of onset of pain medications administered during the postoperative period.

Efficacy and Safety of Ketorolac Tromethamine

Yee et al. (1986) completed a parallel, double-blind comparison study evaluating postoperative pain relief between ketorolac tromethamine and morphine sulfate. Over a period of 6 hours, the analgesic efficacy of intramuscular ketorolac tromethamine, 10 mg, 30 mg, and 90 mg doses was compared to 6 mg and 12 mg doses of intramuscular morphine sulfate. Verbal and visual analog scales were used to assess pain intensity and relief of 241 patients. The authors concluded that 10 mg, 30 mg, or 90 mg ketorolac tromethamine and 12 mg morphine sulfate provided significantly better pain relief than did 6 mg of morphine sulfate. Furthermore, the lower doses of ketorolac tromethamine were equally as effective as the higher dose of morphine sulfate. The higher dose of ketorolac tromethamine was most effective for pain relief during the 6 hour study. Finally, ketorolac tromethamine's rapid onset of action was similar to morphine sulfate.

Brown et al. (1990) conducted a study in which a single intravenous injection of 10 mg ketorolac tromethamine, 30 mg ketorolac tromethamine, 2 mg morphine sulfate, or 4 mg

morphine sulfate was administered to 122 patients selected at random. Comparing efficacy and safety, the authors determined ketorolac tromethamine to be superior in alleviating moderate to severe pain following major orthopedic, abdominal, and gynecologic surgery. The efficacy of pain relief most often followed both doses of ketorolac tromethamine over either dose of morphine sulfate. This response occurred even though the onset of action between the two ketorolac tromethamine doses and 4 mg morphine sulfate were similar. Consequently, the authors concluded that a safer, more effective dose of ketorolac tromethamine can be administered postoperatively versus morphine sulfate which possesses adverse side effects such as respiratory depression.

Pierce, Fragen, and Pemberton (1990) conducted a study comparing ketorolac tromethamine to morphine sulfate, both administered intravenously, for treatment of postoperative pain. In a double-blinded study, 125 female patients undergoing major abdominal gynecologic surgery were selected. Patients were treated with ketorolac tromethamine 10 mg, ketorolac tromethamine 30 mg, morphine sulfate 2 mg, or morphine sulfate 4 mg. The authors concluded that significant differences were lacking in postoperative pain relief between the ketorolac tromethamine and morphine sulfate groups. This was probably related to an inappropriate study design or dosing regimen rather than a

reflection of drug analgesic efficacy. Nevertheless, there was significantly less drowsiness associated with ketorolac tromethamine than with morphine sulfate, indicating less CNS depression.

In a single-blinded, randomized trial by Fernandez-Sabate, Roca-Burniol, Roca-Barbera, and Gonzalez-Caudevilla (1991), the analgesic efficacy of ketorolac tromethamine was compared to metamizole in treatment of pain following orthopedic surgery. Sixty subjects of comparable age, sex, weight, and height, experiencing moderate to severe postoperative pain were used in this well designed study. Ketorolac tromethamine 30 mg was administered IM every 6 hours to 33 patients in one study group; the second group (n = 27) received metamizole, 2 gm, IM every 12 hours. Results demonstrated a greater efficacy of ketorolac tromethamine than metamizole with an acceptable safety profile.

Utilizing 2 case studies, Barton and Elliott (1992) discussed the benefits of ketorolac tromethamine administered to patients 1 hour preoperatively. The authors found that an injection of ketorolac tromethamine 60 mg, IM, provides adequate analgesia without undesirable side effects of respiratory depression, nausea, and vomiting. Furthermore, the authors stated that ketorolac tromethamine's analgesia is superior to that of morphine sulfate without the associated opioid side effects.

Findings from these case studies suggest that ketorolac tromethamine, with a 6 hour half-life, is well suited to provide extended analgesia into the postoperative recovery period. Unlike narcotics, ketorolac tromethamine administration does not promote cardiovascular instability.

Heart rate, mean arterial blood pressure, and arterial partial pressure of carbon dioxide (PaCO2) do not change with a 60 mg, IM, dose of ketorolac tromethamine. Prolonged nausea and vomiting often associated with narcotics given postoperatively does not occur with ketorolac tromethamine, enhancing patient recovery. Ketorolac tromethamine should be used with caution in patients having kidney or hepatic diseases. Careful monitoring is necessary when administering ketorolac tromethamine to patients with coagulation disorders, although the authors emphasize less than 1% of postoperative bleeding is clinically significant. Lastly, ketorolac tromethamine should not be used during labor and delivery since prostaglandin inhibition may adversely effect uterine contractility.

Fernandez-Sabate and Portabella (1991) compared the effectiveness of ketorolac tromethamine to diflunisal in postsurgical orthopedic patients. A total of 100 subjects were used in this multiple-dose, randomized, double-blinded, parallel study. Similar adverse effects were reported using ketorolac tromethamine and diflunisal. These adverse effects included gastrointestinal pain, nausea and vomiting.

More patients who were given diflunisal withdrew from the study than did patients given ketorolac tromethamine because of sequelae of adverse effects. Interestingly, it was also reported that no significant differences in apparent adverse reactions was realized between the 2 groups.

Andujar (1990) conducted a study to determine the analgesic safety and efficacy of ketorolac tromethamine 10 mg and 30 mg, IM, compared to 30 mg, IM of pentazocine. The trial utilized a double-blinded parallel study with a sample size of 149 subjects. No adverse side effects occurred with either drug dosing regime. The study demonstrated that 30 mg, IM, of ketorolac tromethamine was both safe and efficacious and provided a longer duration of postoperative analgesic activity than did 30 mg, IM, of pentazocine.

Ketorolac tromethamine's analgesic effectiveness for pain control following general surgery for orthopedic surgery has been reported to be clinically useful. Kinsella et al. (1992) compared the effectiveness of four, 30 mg doses of ketorolac tromethamine given intramuscularly every 4 hours postoperatively to a placebo. A double-blinded experimental design was utilized. Morphine sulfate, 10 mg, IM, was available upon demand for patients in either the placebo or ketorolac tromethamine group. Data was collected from 30 subjects undergoing major or minor orthopedic procedures using visual analogue pain scores and verbal pain

assessments. Results demonstrated a median reduction of morphine sulfate usage by 33% in patients in the ketorolac tromethamine group undergoing major orthopedic surgery. Significant pain score reduction occurred 4 hours postoperatively in patients receiving ketorolac tromethamine and morphine sulfate versus the placebo and morphine sulfate group. Consequently, the authors concluded that periodic, intramuscular injections of ketorolac tromethamine would be beneficial for postoperative pain relief for major or minor orthopedic surgery.

Cardiorespiratory Effects from Ketorolac Tromethamine

Perioperative hemodynamic effects were examined by Camu, Overberge, Bullingham, and Lloyd (1990) in 18 anesthetized patients following major vascular surgery. A single-dose, parallel-group study was utilized. Ketorolac tromethamine 10 mg and 90 mg, was administered IV postoperatively. Drug effectiveness was evaluated and compared to the effects of 10 mg, IM, morphine sulfate. While morphine sulfate caused a significant reduction in mean arterial blood pressure, left cardiac work index, and left ventricular stroke work index, ketorolac tromethamine had no such cardiovascular effects. The analgesic efficacy of ketorolac tromethamine has been shown to be comparable to the analgesic efficacy of morphine sulfate for moderate to severe postoperative pain. The authors concluded that

present data, as well as existing data, showed that ketorolac tromethamine is safe and does not produce adverse hemodynamic effects as does morphine sulfate.

Kenny, McArdle, and Aitken (1990) compared ketorolac tromethamine and alfentanil in a study regarding cardiorespiratory effects and analgesic efficacy. The subjects (N = 20) were randomly assigned to 1 of 2 groups. Methods of anesthesia were standardized using temazepam as a premedication and propofol as an induction agent. Succinylcholine was the muscle relaxant of choice, and lidocaine spray was used as a topical local anesthetic to augment endotracheal intubation. Each group received either 30 mg ketorolac tromethamine or 0.5 mg alfentanil intravenously on induction of anesthesia. Maintenance of analgesia utilized oxygen, nitrous oxide, and infusion of propofol and alfentanil. Upon achieving cardiorespiratory stability, the alfentanil infusion was discontinued, and the subjects in either group received a bolus of 30 mg ketorolac tromethamine or 0.5 mg alfentanil over 30 seconds. Each group was then monitored for cardiorespiratory changes noting parameters of blood pressure, arterial carbon dioxide, and respiratory rate. The authors illustrated that, unlike the opioid analgesic alfentanil, intraoperative administration of ketorolac tromethamine lacks adverse side effects on heart rate, arterial partial pressure of carbon dioxide, or mean arterial blood pressure. Unlike

alfentanil, ketorolac tromethamine does not cause respiratory depression. The efficacy of pain relief of ketorolac tromethamine and alfentanil was equal. In addition, a decreased frequency of administration of narcotic was required when given concurrently with ketorolac tromethamine. The placebo group self-administered 40% more morphine sulfate by patient controlled analgesia (PCA) than did the ketorolac tromethamine group during the first 24 hours postoperatively. The authors summarized that better pain scores associated with ketorolac tromethamine may be due to a lack of unpleasant side effects as compared to morphine sulfate. They also contend that ketorolac tromethamine's absence of opioid side effects optimizes its use for patients enduring major surgery, both intraoperatively and postoperatively.

Hemostasis Effects from Ketorolac Tromethamine

Greer (1990) analyzed the antiplatelet properties in a double-blind study using 12 healthy volunteers. The results demonstrated ketorolac tromethamine mildly elevates bleeding time. The author concluded however that the prolonged bleeding time probably would be of no clinical significance since almost all coagulation values remained within normal range. He concluded that it would be wise to exert caution if ketorolac tromethamine were used in individuals having coagulation disorders.

Platelet function depends upon the enzyme cyclooxygenase which converts arachidonic acid to endoperoxides prostanglandin G2 and H2. Arachidonic acid is released in the breakdown of a platelet's phospholipid membrane. These factors are then further processed by the enzyme thromboxane synthetase to thromboxane A2. Thromboxane A2 is an important mediator for platelet aggregation during formation of a "platelet plug" necessary for hemostasis (Greer, 1990).

The coagulation effects that ketorolac tromethamine has upon clot elastic strength was studied by Reinhart et al. (1993). Clot elastic strength was analyzed using thromboelastography (TEG) on 20 patients undergoing elective minor surgery. Patients were classified as ASA physical status I or II. Twelve healthy volunteers not receiving surgery were likewise studied in a comparison group. Thromboelastography data collection occurred before administration of ketorolac tromethamine, 60 mg, IM, and 60 minutes after ketorolac tromethamine administration. Thromboelastography data helped determine onset of coagulation, coagulation time, clot formation rate, and maximum clot strength. Ten surgical patients were studied during intraoperative and postoperative periods. Statistical analysis of the data collected showed no significant changes in the clotting parameters which were examined.

Anesthetic Implications

Tourniquet pain is associated with an increase in blood pressure and usually heart rate. No correlation has been found to exist between tourniquet pain and factors such as tourniquet inflation pressure, tourniquet width size, or application of the tourniquet on either right or left extremities. Additionally, increasing tourniquet pressure does not cause a quick onset of tourniquet pain. Generally, an increase in blood pressure and heart rate can be seen 30 to 40 minutes after tourniquet inflation. The type of anesthesia administered influences onset of tourniquet-induced hypertension. Onset of tourniquet-induced hypertension occurred more readily in patients receiving general anesthesia than other forms of anesthesia. Intraoperative hypertension lasts until tourniquet deflation. Tourniquet-induced hypertension is more often associated with longer tourniquet times, in older patients, those with cardiac enlargement, and lower extremity tourniquet application. Studies have shown that higher regional blocks are more effective in controlling tourniquet pain, yet tourniquet pain occurred more slowly with subarachnoid block. Studies related to tourniquet occlusion disagree as to whether increased catecholamine levels are responsible for tourniquet pain. Crews and Selhorst (1991) postulated that a neurohumoral response to tourniquet pressure was related to increased plasma levels of cortisol

and norepinephrine. Conversely, Rocco et al. (1987) concluded that no association existed between plasma catecholamine levels, heart rate, and blood pressure changes upon tourniquet occlusion. Hagenow et al. (1986) stated that additional sources of tourniquet pain resulted from direct pressure on the nerve trunk or from sensory innervation of the vascular bed. The ability to blunt tourniquet-induced hypertension was possibly related to the degree of afferent C-fibers which were blocked. Tourniquet inflation caused a quicker inhibition of A-delta fibers that normally block afferent C-fibers. Therefore, the anesthesic agent's effectiveness and ability to ablate or diminish tourniquet-induced hypertension could be related to the degree of afferent C-fiber blockade.

Studies demonstrate ketorolac tromethamine to be as efficacious or superior to opioid administration. Furthermore, safety concerns reveal ketorolac tromethamine to have fewer side effects than narcotics when given IM or IV. Ketorolac tromethamine has much less CNS depression, nausea, and vomiting than morphine sulfate. Cardiovascular instability or respiratory depression does not occur with administration of ketorolac tromethamine. The onset of action of ketorolac tromethamine is similar to that of morphine sulfate. Due to a 6 hour half-life, ketorolac tromethamine provides effective postoperative pain relief. Adverse physiologic reactions to ketorolac tromethamine,

although infrequent, are generally gastrointestinal in nature. Clinically significant bleeding related to ketorolac tromethamine administration is reported to be less than 1%. Thromboelastography shows that ketorolac tromethamine causes only a mild elevation in bleeding times; most coagulation values remain within normal range. Caution is advised however when administering ketorolac tromethamine to individuals with bleeding coagulopathies.

Indications for Further Study

Tourniquet pain, whether it occurs during regional anesthesia as discomfort to an awake patient, or during general anesthesia as noted by rising blood pressures and heart rate, has been a problem since the inception of tourniquet use to control blood loss. Control of tourniquet pain with repeated administration of opioids or by increasing anesthetic depth with volatile agents, can lead to adverse physiologic sequelae. Prolonged recovery from anesthesia, cardiovascular instability, and respiratory depression are contributing factors to physiologic instability. Anesthetic risk is further increased for those individuals who exhibit chronic respiratory or cardiovascular pathology.

Tourniquet time can be extended with utilization of regional anesthesia. After 90 minutes of tourniquet inflation using regional anesthesia however, tourniquet pain

begins to occur. To date, no definitive treatment exists for relieving tourniquet pain and its physiologic responses other than tourniquet deflation. Preoperative administration of ketorolac tromethamine may delay onset of tourniquet-induced hypertension or pain. Additionally, preoperative administration of ketorolac tromethamine, which has a 6 hour half-life, provides postoperative pain relief.

Proposed Study Methodology

A proposed study group should consist of a minimum of 20 patients randomly assigned to 1 of 2 groups. Patients assigned to the groups should be of either sex, 18 to 65 years of age, and in need of orthopedic surgery requiring a tourniquet on upper or lower extremities. To decrease extraneous variables, only those patients undergoing general anesthesia should be permitted into the study (see Appendix A). The study should be a double-blinded, experimental design, and conducted according to an IRB approved protocol. Those patients selected to the study should receive a standardized explanation followed by a written consent (see Appendix B). Group one should receive a dose of 60 mg ketorolac tromethamine, IV, 60 minutes prior to surgery. Group two should be a control group and receive a placebo, IV, 60 minutes prior to surgery. Medication guidelines for anesthesia induction and maintenance should be standardized and as well allow for individuality of the patient and

anesthetist (see Appendix C). A baseline blood pressure and heart rate should be recorded immediately following tourniquet inflation, and every 5 minutes thereafter. Hypertension should be defined as a 30% elevation from baseline of the systolic blood pressure, diastolic blood pressure, or both for this study. An increase in heart rate 30% above baseline is also defined for identification of tourniquet pain response (see Appendix D). Upon tourniquet inflation, no further narcotics should be administered unless hypertension or tachycardia above 30% of baseline occurs. Total tourniquet time should then be noted upon completion of the study.

Patients should be excluded from the study if diagnosed with overt renal, hepatic, cardiac, neurologic, cerebral, or metabolic disease. Individuals with hypersensitivity to ketorolac tromethamine or other allergic manifestations to aspirin or other NSAIDs should also be excluded from the study. Patients with nasal polyps, asthma or any known history of chronic obstructive lung disease, angioedema, bleeding, psychiatric disorders, alcohol or other drug addictions, gastrointestinal disease or ulcers, pregnancy, use of psychotropic or sedative medications within 6 hours of surgery, those taking hydantoins, anticoagulants, sulfonamides, or other high protein bound medications should be excluded from the study.

Instrumentation

Ten normal saline, 50 ml, IV piggybacks (IVPB) each containing ketorolac tromethamine, 60 mg, and ten placebo IVPBs filled only with normal saline are required. Neither IVPB should be recognizable to the anesthesia provider or patient as to which drug is contained therein. Blood pressure and heart rate values should be measured by basic intraoperative monitors, and may be measured using a blood pressure cuff or intraarterial catheter.

Discussion

Management of patients undergoing surgery with prolonged tourniquet application becomes challenging during general or regional anesthesia. Patients receiving general anesthesia develop hypertension and tachycardia that is refractory to pain relief from narcotics. Patients receiving regional anesthesia complain of extreme discomfort from prolonged tourniquet inflation. Treating tourniquet pain, hypertension, or both with opioids or increasing the depth of general anesthesia leads to adverse anesthetic sequelae after tourniquet deflation, or prolonged recovery from anesthesia postoperatively. In either case, patient care demands increase. A major objective of regional anesthesia is blockade of pain pathways from the operative area. General anesthesia globally blocks pain pathways from

the operative site. Prolonged tourniquet pressure causes pain or hypertension with either regional or general anesthesia. Conditions of regional blockade or general anesthesia will not abate breakthrough tourniquet pain and eventual summation of pain impulses within the nociceptive C-fibers. Tourniquet-induced pain and hypertension occurs with either regional or general anesthesia and may become uncontrollable. The absolute treatment to diminish tourniquet discomfort is to deflate the tourniquet. In most instances, tourniquet-induced hypertension is not a major concern. In patients that are cardiovascularly compromised however, unstable hemodynamic reactions are deleterious to the patient's well-being. Determining whether tourniquet pressure causes release of algogenic substances helps in diagnosing the etiology of tourniquet pain. Preoperative administration of a cyclooxygenase inhibitor, i.e., ketorolac tromethamine will possibly provide pain relief for a longer duration without the occurrence of hypertension during prolonged tourniquet inflation.

Conclusions

The proposed study pertains to preoperative administration of ketorolac tromethamine administered to patients receiving general anesthesia undergoing surgery requiring application of a tourniquet. This approach diminishes several variables concerning methods of

anesthetic administration within the study population. Other methods of anesthetic administration, i.e., regional anesthesia, should not be included in this part of the study. Patient response to tourniquet pressure while under general anesthesia should be documented as hypertension and tachycardia at 30% above baseline values. Ketorolac tromethamine should be administered preoperatively prior to tourniquet inflation because it is a peripherally acting non-steroidal anti-inflammatory drug. Anticipated conclusions of this study will demonstrate that intraoperative tourniquet-induced hypertension and tachycardia will not occur as a result of preoperative administration of ketorolac tromethamine.

A comparison study of patients receiving regional anesthesia undergoing surgery requiring application of a tourniquet could then be compared to the general anesthesia group. It is expected that patients undergoing surgery utilizing a tourniquet and receiving regional blockade would experience progressive tourniquet-induced discomfort. The effectiveness of analgesia from preoperative ketorolac tromethamine administration would be evaluated and compared to the general anesthesia group.

Another study could focus on the mechanism of action of ketorolac tromethamine. Ketorolac tromethamine blocks the action of cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandins. This action may enable

the level of arachidonic acid to increase. The second pathway for metabolism of arachidonic acid involves lipoxygenase, converting arachidonic acid to leukotrienes. Theoretically, this pathway is unopposed from administration of ketorolac tromethamine. Leukotrienes are known mediators of inflammatory and allergic processes. It is possible that patients at risk for adverse reactions from leukotriene-mediated inflammatory processes, i.e., asthmatics, may suffer from administration of ketorolac tromethamine. Documentation of adverse reactions from ketorolac tromethamine may signify that actions of the second pathway, i.e., arachidonic acid to leukotrienes are accountable.

References

References

Assef, S. J. (1991) Carotid Sinus and carotid body physiology. In Faust, R. J. (Ed.), Anesthesiology Review (pp. 181-183). New York: Churchchill Livingston.

Alifimoff, J. K. & Miller, K. W. (1993) Mechanism of action of general anesthetic agents. In Rodgers, M.C., Tinker, J. H., Covino, B. C., & Longnecker, D. E., (Eds.), Principles and Practice of Anesthesiology (pp. 1034-1086). St. Louis: C.V. Mosby.

Andujar, E. G. (1990). Analgesia with ketorolac (Toradol) orthopaedic pain. Clinical Trials Journal, 27(3), 211-218.

Bachhuber, W. L. (Ed.). (1992). Toradol IM and Toradol Oral (Ketorolac Tromethamine) (Product Monograph). Palto Alto, Ca.: Syntex Laboratories, Inc.

Barton, C. R. & Elliott, C. (1992). Ketorolac as a preoperative nonnarcotic analgesic to enhance anesthesia and postanesthesia recovery. Nurse Anesthesia, 3(3), 125-131.

Brown, C. R., Moodie, J. E., Wild, V. M., & Bynum, L. J. (1990). Comparison of intravenous ketorolac tromethamine and morphine sulfate in the treatment of postoperative pain. Pharmacotherapy, 10(6), 116S-121S.

Camu, F., Overberge, L. V., Bullingham, R., & Lloyd, J. (1990). Hemodynamic effects of two intravenous doses of ketorolac tromethamine compared with morphine. Pharmacotherapy, 10(6), 122S-126S.

Cole, F. (1952). Tourniquet pain. Anesthesia Analgesia, 31, 63-64.

Concepcion, M. (1993) Anesthesia for orthopedic surgery. In Rodgers, M.C., Tinker, J. H., Covino, B. C., & Longnecker, D. E., (Eds.), Principles and Practice of Anesthesiology (pp. 2204-2205). St. Louis: C.V. Mosby.

Crews, J. C., Hilgenhurst, G., Leavitt, B., Denson, D. D., Bridenbaugh, P. O., & Stuebing, R. C. (1991). Tourniquet pain: The response to the maintenance of tourniquet inflation on the upper extremity of volunteers. Regional Anesthesia, 16(6), 314-317.

Crews, J. C., & Sehlhorst, C. S., (1991). Response to maintenance of tourniquet inflation in a primate model. Regional Anesthesia. 16(4), 195-198.

Curtis, S. M. (1986) Pain. In Porth, C. M. Pathophysiology: Concepts of Altered Health States (2nd ed.) (pp. 869-887). Philadelphia: Lippincott.

de Jong R. H. (1962). Tourniquet pain during spinal anesthesia. Anesthesiology. 23, 881-882.

Egbert, B. D. & Deas, T. C. (1962). Causes of pain from a pneumatic tourniquet during spinal anesthesia. Anesthesiology. 23(87), 287-290.

Farah, B. A. (1993). Ketorolac in reflex sympathetic dystrophy. Clinical Neuropharmacology. 16(1), 88-89.

Fernandez-Sabate, A. & Portabella, F. (1991). Study of ketorolac tromethamine and diflunisal for pain following orthopaedic surgery. Journal of International Medical Research, 19, 210-218.

Fernandez-Sabate, A., Roca-Burniol, J., Roca-Barbera, A., & Gonzalez-Caudevilla, B. (1991). Ketorolac, a new nonopioid analgesic, in a single-blind trial versus metamizole in orthopedic surgery pain. Current Therapeutic Research, 49(6), 1016-1024.

Floy, B. J., Royko, C. G., & Fleitman, J. S. (1990). Compatibility of ketorolac tromethamine injection with common infusion fluids and administration sets. American Journal of Hospital Pharmacology, 47(5), 1097-1100.

Gissen, A. J., Covino, B. G., & Gregus J. (1980). Differential sensitivities of mammalian nerve fibers to local anesthetic agents. Anesthesiology, 53, 467.

Greer, I. A. (1990) Effects of ketorolac tromethamine on hemostasis. Pharmacotherapy, 10(6), 71S-76S.

Guyton, A. C. (1987). Human Physiology and Mechanisms of Disease. (4th ed.) Philadelphia: W. B. Saunders Co.

Hagenouw, R. P., Bridenbaugh, P. O., Van Egmond, J., & Stuebing, R. (1986). Tourniquet pain: a volunteer study. Anesthesia Analgesia, 65, 1175-1180.

Johansson, S., Josefsson, G., Malstam, J., Lindstrand, A., & Stenstroem, A. (1989). Analgesic efficacy and safety comparison of ketorolac tromethamine and doleron for the alleviation of orthopaedic post-operative pain. Journal of International Medical Research, 17, 324-332.

Jung, D., Mroszczak, E., & Bynum, L. (1988). Pharmacokinetics of ketorolac tromethamine in humans after intravenous, intramuscular and oral administration. European Journal of Clinical Pharmacology, 35, 423-425.

Kapit, W. & Elson L. (1977). The Anatomy Coloring Book. New York: Harper & Row, Publishers.

Kaufman R. D. & Walts L. F. (1982). Tourniquet-Induced Hypertension. British Journal of Anesthesiology, 54, 333-336.

Kenny, G. N., McArdle, C. S., & Aitken, H. H. (1990). Parenteral ketorolac: opiate-sparing effect and lack of cardiorespiratory depression in the perioperative patient. Pharmacotherapy, 10(6), 127S-131S.

Kinsella J., Moffat A. C., Patrick, J. A., Prentice, J. W., McArdle C., & Kenny, G. N. (1992). Ketorolac trometamol for postoperative analgesia after orthopaedic surgery. British Journal of Anesthesiology, 69(1), 19-22.

Kojo, I. & Pertovaara, A. (1986). Effect of tourniquet-induced ischemia on cutaneous thermal thresholds. Acta Neurologica Scandanavia, 74, 383-385.

Lawson, N. W. (1992). Autonomic nervous system physiology and pharmacology. In P. Barash, B. Cullen, & R. Stoelting (Eds.), Clinical Anesthesia (2nd ed.) (pp. 319 -384). Philadelphia: J.B. Lippincott Co.

Longnecker D. E. & Miller F. L. (1993) Pharmacology of inhalational anesthetics. In Rodgers, M.C., Tinker, J. H., Covino, B. C., & Longnecker, D. E., (Eds.), Principles and Practice of Anesthesiology (pp. 1053-1086). St. Louis: C.V. Mosby.

Lubenow, T. R., McCarthy, R. J., and Ivankovich, A. D. (1992). Management of acute postoperative pain. Clinical Anesthesia Updates, 3(4), 1-15.

Melzack, R. (1988). Psychological aspects of pain: implications for neural blockade. In M. J. Cousins & P.O. Bridenbaugh (Eds.), Neural Blockade in Clinical Anesthesia and Management of Pain (2nd ed.) (pp.845-859). Philadelphia: Lippincott.

Morgan, E. G. & Mikhail, M. S. (1992). Clinical Anesthesiology. Norwalk, CT: Appleton & Lange.

Phillips, W.J. (1991). Central nervous system pain receptors. In Faust, R. J. (Ed.), Anesthesiology Review. (pp. 250-251). New York: Churchchill Livingston.

Pearce, C. J., Gonzalez, F. M., & Wallin, J. D. (1993). Renal failure and hyperkalemia associated with ketorolac tromethamine. Archives of Internal Medicine, 153(8), 1000-1002.

Peirce, R. J., Fragen, R. J., & Pemberton, D. M. (1990). Intravenous ketorolac tromethamine versus morphine sulfate in the treatment of immediate postoperative pain. Pharmacotherapy, 10(6), 111S-115S

Reinhart, D. J., Latson, T. W., Whitten, C. W., Klein, K. W., Allison, P. M., & Patel, M. (1993). Influence of ketorolac tromethamine on clot elastic strength in humans as assessed by thromboelastography. Journal of Clinical Anesthesia, 5(3), 216-220.

Rhoades, R. & Pflanzer, R. (1992) Human Physiology (2nd ed.). Ft. Worth: Saunders College Publishing.

Rice, A. S., Lloyd, J., Miller, C. G., Bullingham, R E., & O'sullivan, G. M. (1991). A double-blind study of the speed of onset of analgesia following intramuscular administration of ketorolac tromethamine in comparison to intramuscular morphine and placebo. Anaesthesia, 46(7), 541-544.

Ritcher J. J. (1992). Mechanisms of general anesthesia. In P. Barash, B. Cullen, & R. Stoelting (Eds.), Clinical Anesthesia (2nd ed.) (pp. 129-139). Philadelphia: J.B. Lippincott Co.

Rocco, A. G., Concepcion, M. A., Desai, S., Dhingra, U., & Murray, E. (1987). The effect of general and regional anesthesia on tourniquet-induced blood pressure elevation. Regional Anesthesia, 12(4), 174-180.

Smith, T. C. (1992). Anesthesia and orthopaedic surgery. In P. Barash, B. Cullen, & R. Stoelting (Eds.), Clinical Anesthesia (2nd ed.) (pp. 1215-1235). Philadelphia: J.B. Lippincott Co.

Stevens, W. C. & Kingston, H. G. (1992). Inhalation anesthesia. In P. Barash, B. Cullen, & R. Stoelting (Eds.), Clinical Anesthesia (2nd ed.) (pp. 439-465). Philadelphia: J.B. Lippincott Co.

Stoelting, R. K. (1991). Opioid Agonists and Antagonists. In R. K. Stoelting (Ed.), Pharmacology & Physiology in Anesthetic Practice (2nd ed.) (pp 70-101). Philadelphia: J.B. Lippincott Co.

Strichartz, G. & Zimmerman, M. (1984). An explanation for pain originating from tourniquets during regional anesthesia. Regional Anesthesia, 9, 44-45.

Valli H. & Rosenberg, P. H. (1985). Effects of three anaesthesia methods on haemodynamic responses connected with the use of thigh tourniquet in orthopaedic patients. ACTA Anaesthesiology Scandinavia, 29, 142-147.

Valli, H., Rosenburg, P. H., Kytta, J., & Nurminen, M. (1987). Arterial hypertension associated with the use of a tourniquet with either general or regional anaesthesia. Acta Anaesthesiologica Scandanavia, 31, 279-283.

West, J. B. (Ed.). (1991). Best and Taylor's Physiological Basis of Medical Practice (12th ed.). Baltimore: Williams & Wilkins.

Yee, J. P., Koshiver, J. E., Allbon, C., and Brown, C. R. (1986). Comparison of intramuscular ketorolac tromethamine and morphine sulfate for anagesia of pain after major surgery. Pharmacotherapy, 6(5), 253-261.

Appendices

Appendix A

Guidelines for Tourniquet Pain Study

The purpose of this study is to determine if preoperative intravenous administration of ketorolac tromethamine, a nonopioid, peripherally acting analgesic, can ablate or significantly reduce tourniquet pain in orthopedic procedures.

Patient sample will include:

1. ASA I and II patients
2. Age range: 18-65 years old
3. A procedure that requires a pneumatic tourniquet under general anesthesia on an upper or lower extremity with tourniquet inflation for at least 45 minutes.

Patient sample will **exclude**:

1. Patients with past medical history of hypertension.
2. Patients who are currently taking antihypertensives, beta blocking medications, or both.
3. Patients who have contraindications to intravenous administration of ketorolac tromethamine.
4. Patients receiving regional anesthesia.

Selection of study groups:

1. If the patient meets above criteria, go to pharmacy and assign patient to a study group.
2. Select a single piece of paper that assigns a study group without looking! Give this paper to the pharmacy personnel. The pharmacist will give you an unmarked IV piggyback in return. This IV piggyback will contain either normal saline or 60 mg. of ketorolac tromethamine.

General Rules:

1. Follow guidelines for medication administration during induction and maintenance of anesthesia.
2. Obtain baseline blood pressure and heart rate, which are the vital signs immediately following inflation of the tourniquet.
3. Continue recording BP and HR every 5 minutes.
4. If necessary, you may provide for postop pain relief with drug of your choice, only after tourniquet is deflated or vital signs increase 30% from the baseline values.

Appendix B

CONSENT FORM **IRB #9401-2C**

TITLE: THE ABLATION OR REDUCTION OF INTRAOPERATIVE TOURNIQUET PAIN WITH PREOPERATIVE ADMINISTRATION OF KETOROLAC TROMETHAMINE

Introduction: You are about to undergo orthopedic surgery that will require the use of a tourniquet. During your surgery a tourniquet will be applied to the extremity being repaired. The tourniquet will minimize blood loss and provide the surgeon with a clearer operative field. This study is being conducted to determine if ketorolac tromethamine, given prior to surgery, will prevent or decrease the rise in blood pressure and heart rate caused from tourniquet pressure. Heart rate and blood pressure values will be measured once the tourniquet is inflated.

Patients who consent to participate in this study will be randomly (similar to the flip of a coin) assigned to one of two groups. You will receive either a placebo (inactive substance) or ketorolac tromethamine (pain medication) before surgery begins. Other forms of pain medication will be administered as necessary to minimize discomfort following surgery.

Benefits: With preoperative administration of ketorolac tromethamine you may have less variation in blood pressure and heart rate during surgery. You may also have less postoperative pain and require less medication for pain relief. Your participation in the study may help determine if tourniquet pain can be controlled without increasing anesthetic requirements during surgery.

Alternative Therapy: You do not have to participate in this study. Traditional methods of pain relief will be administered if you choose not to participate.

Risks: Ketorolac tromethamine may prolong bleeding times, or cause an allergic reaction. Ketorlac may not work and pain may still occur postoperatively.

Research Related Injury: In the event of physical and/or mental injury resulting from participation in this research project, Virginia Commonwealth University will not provide compensation. If injury occurs, medical treatment will be available at MCV Hospitals. Fees for such treatment will be billed to you or to appropriate third party insurance. If there are any questions regarding research related risks, they can be directed to the Human Research Committee at 786-0868.

Confidentiality: Your identity will remain confidential. The information obtained in this study may be published but your identity will not be revealed. *The Federal Drug* Administration and the Internal Review Board may also evaluate the records.

Cost of participation: There are no additional costs to participate in this study other than those of the drugs administered. All other medical charges will be billed in normal fashion.

Pregnancy: You should be aware that every effort will be made to have females enter this study on an equal basis with male subjects. Medically accepted birth control is required to enter this study. This may include, but is not limited to, using birth control pills, IUDs, condoms, diaphragms, implants, being surgically sterile, or being in a post-menopausal state. However, no birth control method completely eliminates the risk of pregnancy. If pregnancy occurs there may be a high risk of miscarriage, birth defects, or other unforeseen medical conditions.

Withdrawal: Participation in this study is voluntary. The investigators will answer any questions you may have about the study. You are free to withdraw your consent and discontinue participation at any time. If you decide to withdraw from this study, you should contact Tim Samolitis or Dr. James Embrey. Withdrawal from the study will in no way affect the care you receive now or in the future at this institution. Your physician may also withdraw you for medical reasons. If during the course of the study your medical condition changes, or you experience adverse side effects, your participation may be terminated by the investigator or study sponsor without your consent. Any significant new findings which develop during the course of the research study which may affect your willingness to continue to participate will be provided to you. Questions regarding this study may be addressed to Dr. Embrey (Clinical Director of Nurse Anesthesia) or Tim Samolitis (Senior Nurse Anesthesia Resident) at 828-9808.

I have read and understand the above statements, and I consent to participate in this study.

_____	_____
signature	date
_____	_____
witness	investigator

Appendix C
Medication Guidelines for Study

1. **Pre-op Medication**:

- Sedative: up to 5 mg midazolam, IV

2. **Induction**:

- Defasiculant: 3 mg curare, IV, or
  0.5 mg vecuronium, IV, or
  5 mg atracurium, IV

- Narcotic: 2 - 10 mcg/kg fentanyl, IV (until incision)

- Induction agent: 3 - 5 mg/kg thiopental, IV
  (or up to 500 mg)
  2 - 2.5 mg/kg propofol, IV

- Muscle relaxant: 1 - 1.5 mg/kg anectine, IV, or
  up to 0.1 mg/kg vecuronium, IV, or
  up to 0.5 mg/kg atracurium, IV

  - May use xylocaine up to 1 mg/kg on induction

  - Oxygen at 100%

  - Isoflurane up to 3%

  - Endotracheal intubation

3. **Maintenance**:

- Maintain controlled ventilation via ventilator ($ETCO_2$=30-35).

- Nitrous oxide 60 - 70%, Oxygen 30 - 40% and Isoflurane 0.2 - 1.5% as required to reach steady state.

- After steady state is reached, isoflurane or desflurane cannot be increased and additional fentanyl cannot be given until hypertension is noted.

- For muscle relaxation, titrate atracurium or vecuronium to desired twitch.

- If BP and HR increase by 30% from baseline values, anesthesia provider may treat in usual manner.

Appendix D
Data Collection Form

Patient Chart #_____ Age____ Gender ( ) M ( ) F
ASA ( ) I ( ) II Race ( ) B ( ) W ( ) Ori ( ) Other
Height _____in. Weight _____Kg.
Procedure_____

Surgeon(s)_____ Date_____

Anesthesia
Provider(s)_____

Pre-op: Induction:

( )midazolam ( )anectine ( )isoflurane ( )fentanyl
( )atracurium ( )nitrous oxide ( )thiopental
( )curare ( )oxygen
( )vecuronium
( )xylocaine

Maintenance:
( )air ( )fentanyl ( )atracurium
( )isoflurane ( )vecuronium
( )desflurane
( )nitrous oxide
( )oxygen Amount fentanyl used: _____

Preop BP/HR:_____/_____Baseline BP/HR:_____/_____
(immediately following tourn. inflat.)
Time Tourniquet Up:_____ Time Tourniquet Down:_____

*30% > than baseline **BP/HR**: _____/_____ = *May treat in usual manner.

The following vital signs are **obtained after** tourniquet inflation.

BP/HR: 05 mins:____/___ 10 mins:____/___ 15 mins:____/___

20 mins:____/___ 25 mins:____/___ 30 mins:____/___

35 mins:____/___ 40 mins:____/___ 45 mins:____/___

50 mins:____/___ 55 mins:____/___ 60 mins:____/___

65 mins:____/___ 70 mins:____/___ 75 mins:____/___

80 mins:____/___ 85 mins:____/___ 90 mins:____/___

95 mins:____/___ 100 mins:____/___105 mins:____/___

110 mins:____/___ 115 mins:____/___120 mins:____/___

Vita

Timothy J. Samolitis was born on October 30, 1950 in LaSalle, Illinois, and is an American citizen. He graduated from LaSalle-Peru Township High School, LaSalle, Illinois in 1968. He received an Associate degree in Liberal Arts from Illinois Valley Community College in 1970, and a Bachelor of Science degree in Biology from Loyola University of Chicago in 1973. While serving in the Air Force, he graduated from Wilford Hall Medical Center, San Antonio, as a Laboratory Medical Technologist (MT) in 1976, and became certified by the American Board of Clinical Pathology (ASCP) in 1977. In 1978, he received an Associate degree in Nursing from the University of Alaska while assigned to Elemendorf AFB, Alaska. After being honorably discharged from the Air Force in 1981, he became a laboratory chemistry supervisor at Morris Hospital, Morris, Illinois. In 1988, he received a Doctor of Nursing degree from Case Western Reserve University, Cleveland, Ohio, and was selected as a member of Sigma Theta Tau, the National Honor Society of Nursing. He also received the Marion G. Howell Scholarship for scholastic ability while at Case Western Reserve University. In 1989, he was commissioned as a Second Lieutenant in the United States Air Force. He was assigned to Mather AFB,

California, where he worked as a staff nurse in the intensive care unit. In 1991, he became certified by the American Association of Critical Care Nurses as a critical care registered nurse (CCRN). He was also an instructor of Advanced Clinical Life Support (ACLS) and a physiology instructor for service corpsmen. In 1991, he was selected by the Air Force Institute of Technology to attend graduate school where he is currently pursuing a Master of Science degree in Nurse Anesthesiology at Virginia Commonwealth University, Richmond, Virginia.