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Review Article

Alpha sub 2 -Adrenergic Agonists for Regional Anesthesia: A Clinical Review of Clonidine (1984 - 1995)

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Alpha$_2$ -ADRENERGIC mechanisms of analgesia have been exploited for more than 100 yr. Cocaine, the first spinal anesthetic, produces analgesia primarily by its local anesthetic action, but also inhibits norepinephrine re-uptake, and spinal cocaine produces analgesia, in part, by enhancing noradrenergic stimulation of alpha$_2$ -adrenoceptors. [1] Near the turn of the century, epinephrine was shown to produce spinal analgesia in animals, [2] an effect now recognized to be secondary to alpha$_2$ -adrenoceptor stimulation. [3,4] Nearly 50 yr ago, spinal epinephrine alone was shown to produce clinically useful analgesia, [5] although it is most

commonly combined with local anesthetics for this purpose.

Veterinarians have used alpha$_2$ -adrenergic agonists (xylazine, detomidine, medetomidine) for many years for regional analgesia, but experience with these agents in humans dates back only slightly more than 10 yr. In 1984, Tamsen and Gordh, [7] after testing for neurotoxicity in animals, [6] injected a parenteral preparation of the alpha$_2$ -adrenergic agonist, clonidine, epidurally in two patients with chronic pain. Since then, a complete toxicologic assessment (effects on spinal cord blood flow, [8-10] behavior after lumbar and cervical intrathecal injection in sheep and monkeys, [11,12] and histopathology in sheep, rats, and dogs [11,13,14]) has suggested that clonidine is safe for intraspinal use, and the vast majority of publications examining injectable clonidine for analgesia come from Europe, using their commercially available preparation. In the United States, a preservative-free preparation of clonidine has been submitted to the Food and Drug Administration for approval under the orphan drug indication of epidural treatment for intractable cancer pain.

The goal of this review is to provide a clinically useful synthesis of published experience with clonidine for regional anesthesia, focusing on efficacy when administered alone and in combination with other analgesics in specific patient populations and appropriate monitoring and treatment of side effects. A reasonably comprehensive review of publications through 1995 includes 2,116 patients treated with clonidine via epidural, intrathecal, or peripheral injection (Table 1). Neuraxial administration reports consist primarily of single or multiple boluses for < 24 h (1,437 patients, 77% of total), followed by brief (< 48 h) continuous infusion (270 patients, 15% of total). Prolonged epidural infusion for > 1 week in the treatment of chronic pain represents 148 patients, only 8% of the total.

Route	Patient Population	N
Epidural	Intraoperative and postoperative	605
	Obstetrics	342
	Chronic pain	211
	Pediatrics	126
	Experimental studies	89
Total		1,373
Spinal	Intraoperative and postoperative	409
	Obstetrics	63
	Chronic pain	10
Total		482
Peripheral nerve block	Intraoperative	261

Abstracts published after 1989 and all full-length publications are included.

Table 1

Mechanistic Information

Analgesia

Alpha$_2$ -Adrenoceptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, [15] supporting the possibility of analgesic action at peripheral, spinal, and brainstem sites. Experimental work in animals supports analgesic actions of alpha$_2$ -adrenergic agonists at all three sites, although their relative importance is

controversial. Notably lacking are alpha$_2$ -adrenoceptors on axons of peripheral nerves. Clonidine does produce a minor degree of nerve conduction blockade at high concentrations, however, with some preference for C-fibers. [16-18] This conduction blockade may underlie, in part, the enhancement of peripheral nerve block when this agent is added to local anesthetics (see below).

Several lines of evidence support a spinal action of clonidine in producing analgesia in humans. First, in a study in volunteers, [19] a single lumbar epidural bolus injection of clonidine produced analgesia in the lower, but not upper, extremity against a noxious cold stimulus, as would be anticipated from a spinal action. When clonidine was infused for 4 h in the lumbar epidural space in a subsequent study in volunteers, [20] analgesia spread to the upper extremity, suggesting that more extensive dermatomal distribution of analgesia is possible with continuous infusion.

Second, pharmacokinetic and dynamic analysis supports a spinal site of action of clonidine in humans. After epidural administration in volunteers and patients, clonidine is rapidly absorbed, with peak concentrations in arterial blood within 10 min and in venous blood within 30-45 min (Table 2). Elimination from blood is slow (Table 2) compared with the relatively brief duration of analgesia after epidural clonidine administration (3-5 h), arguing against an action by systemic absorption and redistribution to peripheral or central sites. As expected from these divergent time courses, the correlation between blood clonidine concentration and analgesia within individuals is relatively poor.

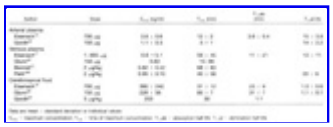


Table 2

In contrast to blood, there is a strong correlation between clonidine concentration in cerebrospinal fluid (CSF) and analgesia after epidural clonidine administration. Clonidine is rapidly and extensively absorbed into the spinal CSF compartment after epidural administration (Table 2), with concentrations peaking 30-60 min after injection. This coincides closely with attainment of near-maximal analgesia. In volunteers, [19] there is a close correlation between lumbar CSF clonidine concentration and analgesia to a noxious stimulus to the lower extremity, with a concentration producing a 95% maximal effect (EC_{95}) of 130 ng/ml (Figure 1). This agrees with the observation in patients after surgery that rescue pain medication usage by patient-controlled analgesia (PCA) approaches zero when calculated CSF clonidine concentrations approach 130 ng/ml (Figure 1). [21] Similarly, the duration of effective analgesia from epidural bolus injection of clonidine, 100-900 micro gram, [22] is in keeping with clonidine's rapid elimination from CSF (Table 2). Duration of complete analgesia in those patients corresponds to the time for CSF clonidine concentrations to decline to 97 plus/minus 52 ng/ml (here and throughout the manuscript, variability is given as plus/minus SD). Finally, computer-controlled infusion of epidural

clonidine to steady state CSF concentrations in volunteers [20] yields a concentration-response for analgesia similar to that obtained in volunteers after bolus administration or in patients after continuous infusion (Figure 1).

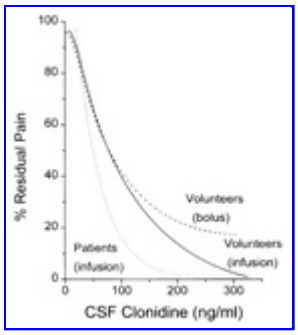


Figure 1

Cerebrospinal fluid is clearly not the site of action of alpha$_2$ -adrenergic agonists for analgesia, and the drug can reach sites producing analgesia in the spinal cord and elsewhere. As with lipophilic opioids, it is possible to achieve analgesia from systemic, epidural, or intrathecal administration of clonidine. However, clonidine is more potent after neuraxial than systemic administration, indicating a spinal site of action and favoring neuraxial administration. This is typified in two types of experiments. In the first, one can compare analgesia from an equal dose of clonidine administered by each of these routes. Therefore, intrathecal injection of a small clonidine dose, 150 micro gram, after cesarean section or minor orthopedic surgery yields analgesia for 4-6 h, but injection of this same dose by intramuscular or epidural routes produces no more analgesia than a placebo (Figure 2). [23,24] Comparing epidural and intravenous administration of a larger clonidine dose, epidural administration produces better analgesia, accompanied by a 50% reduction in rescue morphine requirements. [25] These results are in accordance with a spinal site of action.

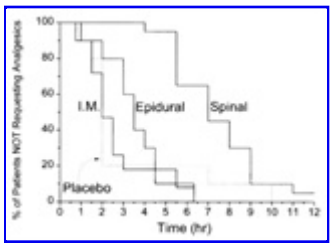


Figure 2

In the second type of study, one can allow patients to titrate drug to similar degrees of pain relief via PCA to compare the relative potency of the drug by different routes of administration. Using this paradigm for opioids, for example, fentanyl is equipotent by intravenous or epidural administration, whereas hydromorphone is approximately twice as potent when given epidurally. [26,27] Using this method, Bernard and colleagues [28] recently demonstrated that clonidine is also approximately twice as potent given epidurally as

intravenously.

Clonidine produces analgesia by actions on alpha$_2$ -adrenoceptors, as shown by partial reversal in humans of epidural clonidine analgesia and sedation, by the alpha$_2$ -adrenergic antagonist, yohimbine, although clonidine's effects on blood pressure and heart rate were not reversed. [29]

In animals, intraspinal alpha$_2$ -adrenergic agonists cause analgesia, in part, by spinal cholinergic activation (Figure 3), [30,31] and two observations suggest this may also occur in humans. First, epidural clonidine, either by bolus [19] or computer-controlled infusion, [20] increases acetylcholine concentrations in lumbar CSF (Figure 3). More precise experiments in animals have demonstrated that this increase is due to release of acetylcholine in the dorsal, but not the ventral, horn. [32] Second, epidural clonidine analgesia in volunteers is enhanced by intrathecal injection of the cholinesterase inhibitor, neostigmine (Figure 3). [33] Whereas this interaction is only additive in humans compared with its synergy observed in animals, it nonetheless supports a reliance on cholinergic mechanisms in spinal analgesia from clonidine.

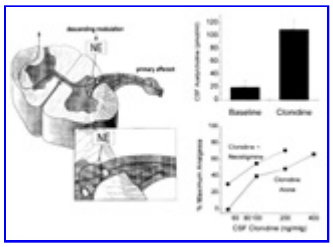


Figure 3

Clonidine enhances both sensory and motor blockade from epidural or peripheral nerve block injection of local anesthetics (see below). Three possible mechanisms for this interaction have been suggested. First, clonidine blocks conduction of C and A delta fibers [17] and increases potassium conductance [34] in isolated neurons in vitro and intensifies conduction block of local anesthetics. [16] Because systemic pharmacokinetics are not a factor in these in vitro experiments, these data support a direct effect of clonidine on neural transmission in high local concentrations, such as may occur after local injection. Second, clonidine may cause local vasoconstriction in the clinical setting, thereby reducing vascular removal of local anesthetic surrounding neural structures. Although clonidine and other alpha$_2$ -adrenergic agonists can vasoconstrict in high concentrations, there is little evidence for this mechanism with clinically used concentrations. For example, plasma lidocaine concentrations are similar whether or not clonidine is combined with lidocaine for epidural anesthesia. [35] In contrast, combining lidocaine with epidural epinephrine does reduce systemic absorption, as reflected in reduced lidocaine concentrations in blood. [35] Finally, it has become evident that analgesics, whether administered systemically or with local

anesthetics, can enhance peripheral or spinal blockade. For example, intravenous or intrathecal fentanyl both enhance intrathecal lidocaine anesthesia, [36,37] and the same is observed with clonidine. [38,39]

Alpha$_2$ -Adrenergic agonists also enhance analgesia from intraspinal opioids. In animals, this interaction occurs both pre- and postsynaptic to the primary afferent synapse in the spinal cord, and is clearly synergistic when both drugs are administered intrathecally. [12,40,41] In contrast, epidural clonidine and fentanyl interact in an additive or only mildly synergistic manner after bolus administration in humans. [42] Nonetheless, the dose of each component can be reduced by more than 60% when epidural clonidine and fentanyl are combined for postoperative analgesia. The type of interaction between clonidine and opioids after intrathecal administration has not been quantified.

Mechanistic studies support a primary spinal site of action of alpha$_2$ -adrenergic agonists for analgesia and a multifactorial mechanism of action in enhancing peripheral or intraspinal blockade from local anesthetics. Pharmacokinetic studies support an EC$_{95}$ of 130 ng/ml clonidine in CSF for analgesia after intraspinal administration and help to clarify the dose responses observed in clinical studies (see below). Opioids and neostigmine enhance intraspinal alpha$_2$ -adrenergic agonist analgesia, and it is likely that a combination of all three classes of agents could result in dramatic reductions in the dose of each.

Hemodynamic Effects

Because systemic absorption of clonidine and other lipophilic alpha$_2$ -adrenergic agonists after spinal administration is rapid and extensive, their hemodynamic effects are due, in part, to actions in the brain and the periphery.

Clonidine affects blood pressure in a complex fashion after neuraxial or systemic administration because of opposing actions at multiple sites (Figure 4). [43,44] In the nucleus tractus solitarius and locus coeruleus of the brainstem, activation of postsynaptic alpha$_2$ -adrenoceptors reduces sympathetic drive. In addition, clonidine is not a pure alpha$_2$ /alpha$_1$ adrenergic agonist; it also activates nonadrenergic imidazoline-preferring binding sites in the lateral reticular nucleus, thereby producing hypotension and an antiarrythmogenic action. [45,46] Blood pressure typically decreases more in hypertensive than in normotensive patients after systemic or epidural clonidine administration, [22] perhaps reflecting increased tonic sympathetic drive in some patients with chronic hypertension. In the periphery, activation of presynaptic alpha sub 2 -adrenoceptors at sympathetic terminals reduces their release of norepinephrine by the sympathetic nerve terminals, which could cause vasorelaxation and reduced chronotropic drive. These brainstem and peripheral effects of alpha$_2$ -adrenoceptor stimulation are counter-balanced by direct peripheral vasoconstriction

from circulating concentrations of the alpha$_2$ /alpha$_1$ adrenergic agonist, clonidine. [47] As a result, the dose response for clonidine by neuraxial or systemic administration is U-shaped, with peripheral vasoconstriction from circulating drug concentrations at high doses opposing central sympatholysis (Figure 4).

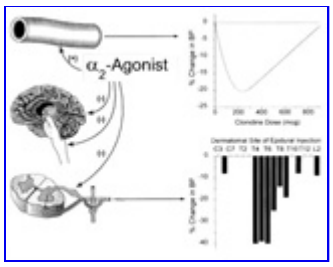


Figure 4

In addition to brainstem and peripheral sites of actions, neuraxial administration of clonidine directly inhibits sympathetic preganglionic neurons in the spinal cord. [48] As a result, the degree of clonidine-induced hypotension is related to the spinal level of injection. At low thoracic or lumbar levels of injection, epidural clonidine is not associated with an increased incidence of hemodynamic side effects when compared with intravenous injection. [25] In contrast, more profound hypotension occurs with thoracic epidural injection (Figure 4), [49,50] perhaps reflecting the rostrocaudal gradient of noradrenergic innervation of sympathetic preganglionic neurons. [51] Alternatively, direct inhibition of sympathetic preganglionic neurons in the upper thoracic dermatomes, which supply the heart, may also have a more profound impact on resting blood pressure than does the inhibition of sympathetic preganglionic neurons elsewhere.

The action of alpha$_2$ -adrenergic agonists on myocardial performance is complex. Clonidine reduces heart rate partly by a presynaptically mediated inhibition of norepinephrine release at the neuroreceptor junction and partly by a vagomimetic effect. Although clonidine depresses atrioventricular nodal conduction, severe bradyarrhythmias are rare with chronic clonidine use. [52] By reducing afterload, cardiac output may increase after clonidine treatment in some patients, including those with heart failure, whereas by reducing heart rate, it may reduce cardiac output in other patients. [53] Clonidine may reduce myocardial oxygen demand and has been shown to reduce infarct size when administered to patients in the acute phase of myocardial infarction. [54] Hemodynamic effects of clonidine after neuraxial or systemic administration begin within 30 min, reach maximum within 1-2 h, and last approximately 6-8 h after a single injection. Delayed onset of hypotension has not been observed with use of clonidine for analgesia alone or in combination (see below).

Combination of an alpha$_2$ -adrenergic agonist with neuraxially administered local anesthetic could increase the degree of sympatholysis and resulting hypotension. However, in clinical studies in which local anesthetic alone was compared with that anesthetic and clonidine

infrequently report significant reduction in arterial blood pressure or heart rate in patients having received the combination therapy (see below). Clonidine has minor or no effects on responses to vasoconstrictors or atropine given to treat hypotension or bradycardia that may occur with neuraxial anesthesia. [55-58] Clonidine pretreatment delays the central nervous system and cardiovascular toxic manifestations of bupivacaine overdose in animals, without accentuating the subsequent hypotension. [59] Treatment with an alpha$_2$ -adrenoceptor agonist during bupivacaine overdose improves the ventricular electrophysiologic parameters in dogs. [60] This is not to imply that clonidine should be used as treatment for bupivacaine overdose, but rather to emphasize that, should such overdose occur, inclusion of clonidine is unlikely to exacerbate the problem.

Spinal neostigmine counteracts the hypotension produced by clonidine, [61] likely due to a cholinergically mediated increase in preganglionic sympathetic nervous system activity. [62] Because neostigmine also enhances clonidine-induced analgesia, [33] this combination may be clinically useful.

Sedation

Sedation commonly accompanies the use of clonidine for regional anesthesia, consistent with the known sedative/anesthetic-sparing properties of alpha$_2$ -adrenergic agonists by actions in the locus coeruleus. [63] This brainstem nucleus is associated with a wide variety of physiologic regulatory processes, including regulation of sleep and wakefulness, and is inhibited by alpha$_2$ -adrenergic agonists via a G-protein mediated mechanism that involves inhibition of adenylate cyclase. [63]

Sedation after epidural administration of clonidine likely reflects systemic absorption and vascular redistribution to higher centers. Although it is conceivable that cephalad migration of clonidine in CSF could result in delayed onset of sedation, such delayed onset sedation has not been observed, nor has delayed-onset hypotension, as described earlier. The more profound depression of electroencephalographic measure of cerebral activity during enflurane/N sub 2 O anesthesia in patients having received epidural compared with intravenous administration [64] could be construed as indicating more profound sedation. However, this more likely represents reduced noxious afferent input to the central sites from a regional spinal effect. Sedation from epidural clonidine represents an alpha$_2$ -adrenergic effect, as witnessed in its reversal by the relatively specific antagonist, yohimbine, in postoperative patients. [29]

Clonidine produces dose-dependent sedation over the dose range 50-900 micro gram of rapid onset (< 20 min) regardless of route of administration. After a large epidural bolus dose (700 micro gram), sedation is intense for 4-6 h. In many cases, sedation is a desired property, and several studies have demonstrated the reduced need for other sedatives and

anxiolytic medications when clonidine is administered intraoperatively. With continuous infusion, as much as 40 micro gram/h epidural clonidine produces no more sedation than epidural placebo plus PCA intravenous morphine for postoperative pain, [21,65] nor does 30 micro gram/h epidural clonidine produce more sedation than epidural placebo plus PCA epidural morphine for cancer pain. [66]

Respiratory Depression

Although there is some evidence that implicates a noradrenergic mechanism of opioid-induced respiratory depression, alpha sub 2 -adrenergic agonists alone do not induce profound respiratory depression, even after massive overdose, [67] nor do they potentiate respiratory depression from opioids. [68,69]

A few studies indicate greater respiratory depression from epidural than from systemic clonidine, but lack of true control groups calls these results into question. [70,71] A study conducted on human volunteers failed to demonstrate any important effect of epidural clonidine on resting respiratory control. [19] However, when considering the respiratory effects of clonidine, it must be considered that drugs acting on the central nervous system to alleviate pain, relieve anxiety, and produce sedation are almost always accompanied by some reduction in alveolar ventilation. As such, it is conceivable that clonidine therapy, by causing pain relief, could unmask respiratory depression from other drugs administered concurrently. Occasional reports of intermittent upper airway obstruction during deep sedation with clonidine, accompanied by transient oxyhemoglobin desaturation, suggest that monitoring with pulse oximetry may be indicated for 30 min to 2 h after large bolus doses. Two human volunteer studies specifically addressed the question of the potentiation of the respiratory depressant effects of opiates by the $alpha_2$ -adrenoceptor agonists. Absolutely no potentiation of this effect could be demonstrated. [68,72] As will be noted later, oxyhemoglobin desaturation is less likely with an epidural clonidine-opioid combination than with opioid alone.

Hormonal Effects

Clonidine is a potent sympatholytic agent, as discussed earlier. In stress situations, it reduces, but does not suppress, the neurohormonal secretion (norepinephrine, epinephrine, adrenocorticotrophic hormone, cortisol) secondary to sympathoadrenal hyperactivation. [73,74] $alpha_2$ -Adrenergic agonists promote the release of growth hormone, but this effect is short lived. [75] They also inhibit the release of insulin by a direct action on the cells of the islets of Langerhans, although this effect is minor and devoid of clinical consequences. [22]

Epidural Administration

By far, the largest reported experience with clonidine for regional anesthesia is with epidural administration. Following is a review of published reports of epidural clonidine treatment for chronic pain, intra- and postoperative pain, and in obstetric and pediatric patients, followed by suggested guidelines in the use of epidural clonidine.

Chronic Pain (240 Patients Total, 211 Receiving Clonidine)

Reasons for the use of epidural clonidine in patients with chronic pain are several: avoidance of opioids because of concerns over addiction in patients with nonmalignant conditions or when opioids cause therapy-limiting side effects, efficacy in cases of reduced potency of opioids due to development of tolerance or in pain syndromes poorly responsive to opioids, and specific indications of neuropathic or sympathetically maintained pain.

Cancer Pain (123 Patients Total, 94 Receiving Clonidine). [66,76-80] Epidural clonidine is indicated in the treatment of intractable pain, which is the basis for approval of clonidine in the United States. In the pivotal trial underlying this indication, [66] 85 patients with severe cancer pain unresponsive to maximally tolerated doses of oral or epidural opioids were randomized to receive epidural 30 micro gram/h clonidine or a placebo, in a double-blind, multicenter study. All patients received rescue pain medication (epidural morphine) by PCA, and success was defined as a reduction in either epidural morphine use or visual analog scale (VAS) pain, with the other variable not increasing. Success was more common in patients receiving clonidine (45%) than placebo (21%), and average VAS pain scores were reduced in patients receiving clonidine (Figure 5). Clonidine was particularly effective in patients with neuropathic pain (36 patients total, 56% success with clonidine vs. 6% with placebo).

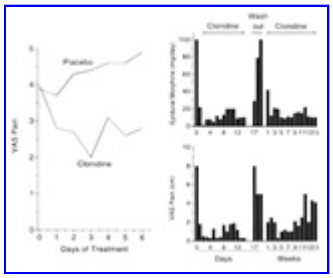


Figure 5

After completion of the 2-week blinded study, patients were allowed to receive continuous epidural clonidine infusion in an open-label manner. Thirty-five patients received clonidine for an average of 8 weeks (1-94 weeks) before their death. An example of VAS pain in a patient with neuropathic pain who received epidural clonidine in the blinded and open-label portions of the study, separated by the obligatory 3-day washout between the study parts, demonstrates the dramatic response observed in many patients (Figure 5).

Five uncontrolled studies of 38 patients with intractable pain support the results of this trial. [76-80] For example, epidural clonidine bolus produced dose-dependent analgesia in 9 patients with cancer receiving 100-900 micro gram, and continuous infusion of 12.5-70

micro gram/h for as long as 94 weeks resulted in sustained analgesia during the period of infusion. [77] In only 1 of the 38 reported patients was epidural clonidine considered ineffective. [80]

Although the vast majority of patients in the double-blind trial of epidural clonidine for cancer pain experienced side effects, there was no difference in the incidence of side effects between clonidine and placebo. [66] Clonidine decreased blood pressure by 10-20%, but hypotension led to discontinuation of the drug in < 10% of cases. Although sedation was noted on initiation of clonidine therapy, this rapidly decreased, and there were no differences in sedation between clonidine and placebo treatments during the 2-week trial. Nausea was less in patients receiving clonidine plus rescue morphine than in those receiving placebo plus rescue morphine. These observations of mild hypotension and transient sedation from epidural clonidine are supported in the uncontrolled studies.

Chronic Noncancer Pain (128 Patients Total, 117 Receiving Clonidine). [7,50,81-88] There are few controlled studies of epidural clonidine for chronic non-cancer pain, and all but one examined single boluses of small doses (25-150 micro gram). Glynn and colleagues [85] used a randomized, double-blind design to compare 150 micro gram epidural clonidine to 5 mg epidural morphine in patients with chronic low back pain or pain from arachnoiditis. Clonidine relieved pain in 16 of 20 patients, was as good or better than epidural morphine, and produced fewer side effects than morphine. These results were supported in their open-label studies of 25 patients with deafferentation pain after spinal injury [82,84] and 20 patients with chronic pain, primarily of the lower back. [86] These open-label trials should, however, be viewed with caution, because this group failed to demonstrate efficacy from epidural clonidine in a double-blind trial of patients with low back pain who had reported analgesia from clonidine in a previous open-label study. [87] Similarly, Taniguchi et al. [81] reported excellent pain relief from thoracic epidural injection of extremely small doses (25-75 micro gram) of clonidine in 10 patients with postherpetic neuralgia. Whether this reflects exquisite sensitivity of this pain syndrome to clonidine or is an artifact of the open-label design awaits further testing.

Clearly, some patients with chronic pain obtain relief from regional sympatholysis, and the syndrome of sympathetically maintained pain is classically considered to consist of altered neural function at three sites: sensitivity to norepinephrine at peripheral primary afferent terminals, recruitment of large diameter fibers in pain perception at dorsal horn sites, and enhanced sympathetic outflow from the spinal cord. $alpha_2$ -Adrenergic agonists could reduce pain in such states by actions at all three sites: reduction in peripheral norepinephrine release by stimulation of prejunctional inhibitory alpha sub 2 -adrenoceptors, inhibition of noxious neural transmission in the dorsal horn by both pre- and postsynaptic mechanisms, and direct inhibition of spinal preganglionic sympathetic neurons.

Clinical experience suggests that epidural clonidine is effective in patients with

sympathetically maintained pain. Epidural clonidine, 300 and 700 micro gram, produced analgesia as assessed by VAS and McGill Pain Questionnaire measures in 26 patients with the clinical diagnosis of reflex sympathetic dystrophy in a double-blind, placebo-controlled trial. [50] Neither sedation nor hypotension from epidural clonidine was more severe with cervical, compared with lumbar, injection. Nineteen patients in this study then received continuous epidural clonidine infusion in an open-label manner for 43 plus/minus 35 days (range 7-225 days). Clonidine usage averaged 32 plus/minus 26 micro gram (range 14-50 micro gram/h), and VAS pain during this open-label phase was significantly reduced (5.1 plus/minus 2.6) compared with their VAS pain before the study (7.9 plus/minus 1.7).

It has been suggested that certain chronic pain syndromes, such as phantom limb pain after amputation, are due to plastic changes that occur in the spinal cord in response to peripheral neural injury and deafferentation, and that preemptive block of afferent input by neuraxial analgesia may block development of such pain. This is supported by a small clinical study in which 24 patients scheduled to undergo lower limb amputation were randomized to receive no preoperative epidural treatment or 24 h of epidural infusion of a combination of diamorphine, bupivacaine, and clonidine, extending for 72 h after amputation. [88] The incidence of phantom limb pain 1 yr after surgery was reduced from 73% in the control group to 8% in the epidural treatment group. The relative contribution of clonidine to this dramatic protection against this chronic pain awaits further study.

Perioperative Use in Adults, Excluding Obstetrics (1,048 Patients Total, 605 Receiving Clonidine)

The large number of studies (29) in the perioperative period probably reflects the ease of studying this patient population. Most controlled, double-blind studies in this group demonstrate efficacy and specific advantages of clonidine over traditional agents, and these studies do not demonstrate hemodynamic instability from epidural clonidine.

Pre- and Intraoperative Use (285 Patients, 148 Receiving Clonidine). [34,49,64,71,89-92] Systemically administered alpha$_2$ -adrenergic agonists have been advocated for premedication before surgery to provide sedation without respiratory depression. In the only study of epidural clonidine (300 micro gram) premedication, Penon et al. [71] observed intense sedation 60-120 min after injection in 7 patients, accompanied by decreased blood pressure (by 13-25%) and heart rate (by 10-16%). Although snoring was observed in five of these seven patients, and ventilatory response to inhaled carbon dioxide was mildly depressed, clonidine did not alter end-tidal carbon dioxide, and all patients had oxyhemoglobin saturation > 95% without supplemental oxygen.

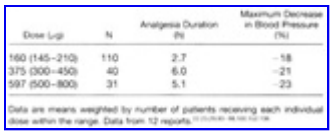
The use of epidural clonidine as a supplement to general anesthesia has been the subject of few reports. In a double-blind, placebo-controlled trial, 300 micro gram epidural clonidine reduced intraoperative intravenous fentanyl requirements by 50% and provided postoperative analgesia for 4 h, without significantly reducing blood pressure. [89] Although

systemic administration of clonidine also reduces anesthetic requirements, De Kock et al. [64] demonstrated that 8 micro gram/kg epidural, but not intravenous, clonidine reduced total power of the electroencephalogram as a measure of anesthetic depth in women anesthetized with enflurane for vaginal hysterectomy. This same group demonstrated a 50-75% reduction in supplemental propofol and alfentanil use when clonidine was infused epidurally, compared with the same dose intravenously during surgery. [25]

Clonidine prolongs and intensifies anesthesia from epidural local anesthetics without increasing hypotension during surgical epidural anesthesia. For example, 150 micro gram clonidine triples duration of anesthesia from 10 ml 0.5% bupivacaine in patients undergoing hip surgery (5.3 plus/minus 0.9 h vs. 1.8 plus/minus 0.3 h), without affecting onset. [92] Motor and sensory block are enhanced by clonidine (see obstetric use below). Clonidine, 150-600 micro gram, added to epidural bupivacaine [92] or lidocaine [35] for surgery does not reduce blood pressure more than local anesthetic alone, and does not diminish the blood pressure response to ephedrine. Addition of clonidine produces sedation but no change in respiratory rate or arterial partial pressure of oxygen or arterial partial pressure of carbon dioxide. Clonidine also produces analgesia beyond the duration of local anesthetic effect, as exemplified by the longer time to first analgesic requirement (13 plus/minus 4 h vs. 7 plus/minus 5 h) when 150 micro gram clonidine was added to a caudal lidocaine/bupivacaine/epinephrine mixture for anal surgery. [91]

Postoperative Use (763 Patients Total, 457 Receiving Clonidine). [22,23,28,29,93-109] In 21 studies, 18 of them with active or placebo controls, the safety and efficacy of epidural clonidine alone or in combination with opioids or local anesthetics for postoperative analgesia were examined. Approximately two thirds of patients who were studied received single or multiple boluses, with the remainder receiving continuous epidural infusion for 24-72 h. Epidural clonidine clearly produces analgesia and reduces the need for other agents, and there has been no case of serious hemodynamic or respiratory depression in this large experience.

Duration of analgesia, defined as the time from epidural bolus clonidine administration until first request for pain medicine, demonstrates analgesia of 2-6 h with no increase in duration beyond a dose of 400 micro gram (Table 3). This duration of analgesia is similar to lipid soluble opioids but briefer than morphine. For this reason, continuous infusion is required for sustained analgesia. After a loading dose of 417 micro gram, patients administer 24 plus/minus 14 micro gram/h epidural clonidine by PCA to achieve analgesia after scoliosis surgery. [28] Similarly, 25 micro gram/h epidural clonidine is equipotent to epidural morphine, 1 mg bolus plus 0.1 mg/h in patients after total hip replacement, whereas 50 micro gram/h clonidine was more potent in reducing rescue analgesic requirements. [109] A much larger epidural clonidine infusion rate (120-150 micro gram/h) provided complete analgesia in patients after major abdominal procedures. [99]



Dose (μg)	N	Analgesia Duration (h)	Maximum Decrease in Blood Pressure (%)
160 (145–210)	110	2.7	−18
375 (300–450)	40	6.0	−21
697 (500–800)	31	5.1	−23

Data are means weighted by number of patients receiving each individual dose within the range. Data from 12 reports.

Table 3

Side effects commonly observed after epidural clonidine in postoperative patients are hypotension, bradycardia, sedation, and dry mouth. After bolus administration, epidural clonidine causes a dose-independent reduction in blood pressure (Table 3) and a 5-20% reduction in heart rate. In the 181 patients receiving bolus epidural clonidine after nonobstetric surgery who are summarized in Table 3, only 1% received treatment with atropine for bradycardia and, although many received intravenous fluids for reduced blood pressure, none received intravenous vasoconstrictors. In contrast, none of the 92 patients receiving epidural clonidine by continuous infusion or PCA received treatment for bradycardia, but 8 (9%) received vasoconstrictor treatment for hypotension. Sedation is common with bolus administration, lasting 1-2 h after 150 micro gram clonidine and 2-4 h after 400 micro gram, but is uncommon with continuous infusion. None of these patients had evidence of respiratory depression by pulse oximetry, arterial or end-tidal carbon dioxide, or respiratory rate monitoring.

In animals, alpha$_2$ -adrenergic agonists and opioids interact synergistically for analgesia after intraspinal, but not systemic, injection, [41] and epidural clonidine has been combined with fentanyl, sufentanil, butorphanol, and morphine for postoperative analgesia. Epidural clonidine, 150 micro gram, increased the duration of analgesia from fentanyl 100 micro gram more than twofold to 9 h in patients after abdominal aortic surgery, [103] and 21 micro gram/h epidural clonidine infusion reduces epidural fentanyl infusion requirements by 45% after colorectal surgery. [108] For sufentanil, an addition of 70 micro gram epidural clonidine to 25 micro gram sufentanil produces longer analgesia (4.2 plus/minus 3.1 h) than 50 micro gram sufentanil alone. [104] In animals, spinal alpha$_2$ -adrenergic agonists interact synergistically with micro but not all opioid subtypes, [110] and this may explain the lack of enhancement in humans from 75 micro gram epidural clonidine added to 0.5 mg butorphanol. [105]

Epidural clonidine has been combined with morphine in four double-blind, controlled studies in postoperative patients. [102,106,107,109] Whereas a single bolus of 75 micro gram clonidine did not affect analgesia from 3 mg epidural morphine after meniscectomy, [102] larger doses (150 and 280 micro gram) did enhance analgesia from morphine (1 and 2 mg, respectively) after total hip replacement [109] and pancreatectomy. [106] This discrepancy may reflect the brief and minimal analgesia from 75 micro gram clonidine alone, which may have dissipated before the slow-onset morphine had taken effect. In both studies with larger clonidine doses, onset of effective analgesia was more rapid with clonidine-morphine (< 30 min) than with morphine alone (> 60 min). Because the time course of action differs so widely between clonidine and morphine, their interaction could more easily be investigated

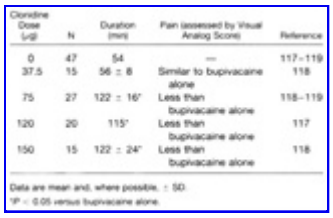
during continuous infusion. Motsch et al. [107] demonstrated that addition of 19 micro gram/h continuous epidural clonidine infusion reduced pain scores, reduced by > 50% the use of supplemental analgesics, and improved forced vital capacity when added to epidural morphine (0.25 mg/h for 24 h, then 0.17 mg/h for 24 h, then 0.08 mg/h for 24 h).

Epidural clonidine has also been combined with local anesthetics alone and with morphine for postoperative analgesia. Addition of 150 micro gram clonidine to 9 ml 0.25% bupivacaine during total hip replacement under general anesthesia doubled the duration of postoperative analgesia compared with bupivacaine alone (4.3 plus/minus 2.3 vs. 2.0 plus/minus 0.9 h) and reduced pain scores. [100] In this study, patients received 0.1 mg/h epidural morphine at the first request for pain, and patients who received clonidine plus bupivacaine required 60% less systemic rescue pain medication than those who received bupivacaine alone. Clonidine did not alter the incidence of hypotension or bradycardia from bupivacaine. Similarly, addition of 18.75 micro gram/h epidural clonidine to a postoperative infusion of 5 mg/h bupivacaine plus 0.1 mg/h morphine reduced pain during mobilization and coughing compared with bupivacaine plus morphine alone. [101]

Obstetric Use (606 Patients, 342 Receiving Clonidine)

Epidural and intrathecal clonidine do not affect uterine blood flow or produce signs of fetal stress in pregnant sheep. [111,112] Although intravenous clonidine increases uterine tone and produces maternal and fetal hypoxemia, [113] these results are due to an unusual platelet response to alpha$_2$ -adrenergic agonists in this species. [114] These preclinical toxicity studies have been followed by a series of clinical studies of the use of neuraxial clonidine in obstetrics.

Labor (222 Patients, 114 Receiving Clonidine). [115-119] Because it was recognized that the dose of epidural clonidine alone necessary to provide effective labor analgesia would be accompanied by unwanted sedation and hypotension, clinical experience has been restricted to combinations of clonidine with bupivacaine. Table 4 summarizes the duration of analgesia from three controlled trials of 124 women in which 0.125% bupivacaine was injected alone or with clonidine. [117-119] These data demonstrate that 37.5 micro gram clonidine does not affect duration of analgesia, whereas a similar doubling in analgesia duration occurs with clonidine doses of 75-150 micro gram. Motor block and maternal blood pressure were unaffected by the addition of clonidine, but transient maternal sedation and reduced maternal heart rate were noted with clonidine doses greater than 100 micro gram. Taken together, these data suggest that 75 micro gram may be an appropriate dose to combine with bupivacaine as a single bolus.



Clonidine Dose (μg)	N	Duration (min)	Pain (assessed by Visual Analog Score)	Reference
0	47	54	—	117–119
37.5	15	56 ± 8	Similar to bupivacaine alone	118
75	27	122 ± 16*	Less than bupivacaine alone	118–119
120	20	115*	Less than bupivacaine alone	117
150	15	122 ± 24*	Less than bupivacaine alone	118

Data are mean and, where possible, ± SD.
*P < 0.05 versus bupivacaine alone.

Table 4

These data are supported by comparisons of the effects of clonidine to sufentanil when added to bupivacaine. For example, Cigarini et al. [115] observed longer analgesia from the addition of 75 micro gram clonidine to 12.5 mg bupivacaine for labor analgesia than from 10 micro gram sufentanil with similar analgesia in the clonidine group to those receiving both 10 micro gram sufentanil and 12.5 micro gram epinephrine with bupivacaine. Pain scores were lower in the clonidine group than in the others. Le Polain et al. [116] confirmed that a small clonidine dose (30 micro gram) was ineffective in increasing the duration or intensity of a bupivacaine-sufentanil-epinephrine combination in labor.

Maternal side effects of epidural clonidine in labor mirror those in other patient populations. Sedation is not evident in doses less than 100 micro gram. Hemodynamic side effects are comparable in all studies to those of the plain local anesthetic. One observed event, a significant decrease in maternal heart rate 30-90 min after first bolus injection, [117] was mild and clinically unimportant. Duration of labor was prolonged after epidural clonidine compared with control in one study of 22 patients. [119] However, there is no physiologic basis to predict a prolongation of labor from epidurally administered alpha$_2$ -adrenergic agonists, and because duration of labor was unaffected by clonidine in the other trials, [115-118] it is unlikely that clonidine would affect this parameter.

Clonidine has been used for many years to treat hypertension during pregnancy. [120] Although it is conceivable that it may be used safely for analgesia during labor, it is known that transplacental transfer is extensive after oral [120] and epidural [119] administration. In one study, [119] fetal heart rate increased from 138 plus/minus 3.2 to 145 plus/minus 3 beats/min 1 h after epidural bupivacaine injection, but decreased from 138 plus/minus 3.2 to 134 plus/minus 2.5 beats/min after epidural bupivacaine plus clonidine. However, no abnormal fetal heart rate tracings were noted. In all the remaining studies in which epidural clonidine was administered, neither fetal heart rate nor Apgar scores revealed any significant abnormalities related to clonidine.

Cesarean Section (384 Patients, 228 Receiving Clonidine). [21,42,65,70,121-123] Although the experience of epidural clonidine for analgesia after cesarean section is similar to that reviewed above after other surgical procedures, it is separated out for two reasons. First, it is conceivable that pregnancy-induced changes could alter the dose response of epidural clonidine for analgesia or hemodynamic effects. Second, this is a very uniform group of healthy patients with a single operation, an ideal group in which to summarize effects of an

analgesic therapy.

Clonidine alone (150-300 micro gram) produces only 3-4 h of analgesia after cesarean section, [70] necessitating continuous infusion for sustained analgesia. Infusion rates of epidural clonidine alone of 10-40 micro gram/h demonstrated dose-dependent analgesia, defined by reduction in supplemental PCA morphine use (percent reduction in morphine: 18 plus/minus 10% after 10 micro gram/h; 53 plus/minus 8% after 20 micro gram/ml; 65 plus/minus 9% after 40 micro gram/ml), with the highest infusion rate reducing supplemental morphine use to a similar extent to a single 5-mg bolus of epidural morphine. [21,65] Analgesia was equivalent in these studies, whether a 400- or 800-micro gram loading dose was administered, despite more sedation during the first 3 h from the larger loading dose, suggesting superiority of a loading dose of 400 micro gram. This agrees with a dose ranging study, demonstrating the effective single bolus dose without infusion to produce analgesia in 50% of women after cesarean section (ED50) to be 353 micro gram. [42] Use of 2-chloroprocaine for epidural anesthesia diminishes analgesia from subsequently administered epidural clonidine, similar to that observed with opioids. [65]

Clonidine has also been combined with opioids for postcesarean section analgesia. Using an epidural PCA design, Vercauteren et al. [122] demonstrated a 33% reduction in sufentanil usage (to 5.8 micro gram/h) when clonidine was added (average clonidine usage, 8.7 micro gram/h). The groups did not differ in sedation, but 10% of those receiving clonidine had hypotension treated with intravenous fluid administration. Using a single bolus isobolographic design, Eisenach et al. [42] demonstrated a marked reduction in the ED50 of epidural clonidine (from 353 to 98 micro gram) when combined with fentanyl. Capogna et al. [121] compared analgesia from a solution of 12.5 mg bupivacaine, 12.5 micro gram epinephrine, and 2 mg morphine alone by intermittent bolus dosing on demand and from the addition of 75 and 150 micro gram clonidine. Surprisingly, given clonidine's relatively brief duration of action alone, addition of clonidine produced a dose-dependent increase in duration of analgesia from morphine (6.3 plus/minus 1.6 h after morphine solution alone, 13 plus/minus 3.8 h with 75 micro gram clonidine, 22 plus/minus 6.3 h with 150 micro gram clonidine) and reduction in morphine use for 36 h. Average clonidine use was 5 micro gram/h in the 75-micro gram group and 7.5 micro gram/h in the 150-micro gram group.

Clonidine-induced side effects appear similar in women after cesarean section as in other postsurgical populations. When injected in the presence of an existing bupivacaine block, clonidine (400 and 800 micro gram) prolongs duration of both motor and sensory blockade, [65] which could delay discharge from the recovery room. Dose-dependent sedation is present with boluses greater than 100 micro gram, but is no different than placebo with continuous infusions of 10-40 micro gram. Narchi et al. [70] observed periods of obstructive apnea with oxygen saturation less than 90% in 3 of 6 women within 30 min of a bolus dose of 300 micro gram, whereas other investigators observed no such desaturation in 140 women receiving bolus doses of 400-800 micro gram. [21,42,65] Clonidine produced

hypotension that required treatment (usually intravenous fluid administration) in 2-10% of women after cesarean section in these studies.

Pediatric Use (280 Patients, 126 Receiving Clonidine) *RF 124-130*

([124-130]) Epidural clonidine (1-5 micro gram/kg) enhances the effect of bupivacaine for caudal analgesia in the postoperative setting in children (mean age of children in these studies ranged from 3.2 to 6 yr). Addition of 1 micro gram/kg clonidine to 1 ml/kg 0.125% bupivacaine increased the duration of postoperative analgesia more than twofold compared with bupivacaine with or without the admixture of epinephrine (16 plus/minus 10 vs. 6.2 plus/minus 5.7 and 7.6 plus/minus 7.3 h, respectively). [125] Similarly, addition of 2 micro gram/kg epidural clonidine to 0.25% bupivacaine doubles duration of analgesia compared with bupivacaine alone. [124,130] In another study, in which 2 micro gram/kg clonidine was used, lower pain scores were obtained 270 min after injection, compared with 0.25% bupivacaine, with or without the addition of epinephrine. [126] Similarly, 3 micro gram/kg clonidine increased by 50% the duration of postoperative analgesia from caudal bupivacaine in children. [128] Adding 5 micro gram/kg clonidine to 1 ml/kg of a more dilute bupivacaine solution (0.1%) resulted in equivalent analgesia, defined as number of requests and total amount of intravenous PCA tramadol, to 0.175% bupivacaine without clonidine. [127] Hemodynamic depression after 5 micro gram/kg epidural clonidine was significantly more pronounced during the first 4 h, whereas studies using lower doses of clonidine found no difference in blood pressure and heart rate compared with control caudal analgesia.

Intrathecal Administration

As previously noted with opioids, the dose of drugs of moderate to high lipophilicity, such as fentanyl or sufentanil, required for analgesia may not be reduced by epidural compared with systemic administration, [26,131] due to rapid systemic absorption after epidural injection and nonspecific binding to epidural fat. In contrast, significant dose-sparing compared with systemic administration is observed when fentanyl or sufentanil are given intrathecally. [132,133] Given clonidine's lipophilicity (similar to fentanyl), one would expect its spinal effects to be more pronounced and selective after intrathecal rather than epidural administration.

Chronic Pain (10 Patients, All Receiving Clonidine) *RF 134-140*

([134-140]) Intrathecally administered clonidine has been reported in anecdotal form in only ten patients, nine of whom had cancer pain. Clonidine was administered in bolus doses of 30-150 micro gram and in continuous infusions of 8-400 micro gram/day, usually in combination with morphine, and was reported to improve pain relief in 9 of 10 cases. Duration of therapy was 1 day to 3 months, and histopathologic examination of the spinal cord revealed no evidence of neurotoxicity in two patients who had received long-term

intrathecal clonidine therapy for cancer pain. [135,137] One patient reported severe pain on injection of 75 micro gram clonidine, [138] and there was a high incidence (30%) of hypotension or bradycardia that required ephedrine or atropine. Therefore, experience in this patient population is too limited to establish the use or safety of intrathecal clonidine for chronic pain.

Intra- and Postoperative Use (870 Patients, 409 Receiving Clonidine) *RF 38,92,141-156*

([38,92,141-156]) Only one study has tested the ability of intrathecal clonidine alone to provide surgical anesthesia. [152] Just as with the experience with intrathecal opioids, large doses of clonidine (as much as 450 micro gram), although providing sedation and intense and long-lasting postoperative analgesia (see Obstetric Use later [157]), are inadequate for surgical anesthesia. For this reason, clonidine has been used as an adjunct to local anesthetics rather than alone.

Clonidine has been demonstrated repeatedly to prolong sensory and motor block from intrathecal local anesthetics. For example, 178 patients from 5 studies, [141,143-146] randomized to receive spinal 13.75-15 mg bupivacaine alone or with clonidine (mean dose 146 micro gram, range 75-225 micro gram) experienced 31% longer sensory and motor block when clonidine was added (mean duration of sensory/motor block with bupivacaine alone of 2.5/2.4 h compared with 3.7/3.3 h with clonidine). Similar results are reported with addition of clonidine to smaller doses of bupivacaine, [92,142,145,148-150,153-155] tetracaine, [38,151] or meperidine. [147] Of potential relevance to the combined spinal-epidural technique in laboring women, combination of 60 micro gram clonidine with 2.5 mg bupivacaine intrathecally yielded 7.4 plus/minus 4.9 h of analgesia, without motor block or hemodynamic changes in patients undergoing anal surgery, in comparison with 4.7 plus/minus 1.4 h of analgesia from bupivacaine alone. [142]

Like intrathecal opioids, clonidine intensifies spinal anesthesia from bupivacaine, thereby reducing the incidence of tourniquet pain. [141] Although the mechanism of clonidine's enhancement of spinal local anesthetics is unknown, it is probably not due to altered systemic absorption, because plasma pharmacokinetics of bupivacaine after spinal injection are unaffected by addition of clonidine. [153] Unlike spinal opioids, clonidine does not cause urinary retention, and may actually hasten time to first micturition after spinal anesthesia. [148,150]

Intrathecal injection of local anesthetics reduces blood pressure primarily by reducing sympathetic outflow. Because this effect is near maximal with doses of local anesthetics causing surgical anesthesia, one would not expect greater degrees of hypotension from clonidine-induced sympatholysis when it is added to local anesthetics. Indeed, maximal decreases in blood pressure and incidence of treatment with vasoconstrictors are only slightly increased from addition of 75-225 micro gram clonidine to 15 mg bupivacaine (18%

decrease in blood pressure and 24% incidence of ephedrine treatment with bupivacaine alone compared with an 18% decrease in blood pressure and 35% incidence of ephedrine treatment with bupivacaine plus clonidine [n = 178]). [141,143-146] In contrast, with a smaller dose of bupivacaine (5 mg), which itself only reduces blood pressure by 10%, the addition of 150 micro gram clonidine does cause a greater decrease in blood pressure (by 30%). [92]

Obstetrics (88 Patients, 63 Receiving Clonidine) *RF 24,157-159*

Labor (38 Patients, 23 Receiving Clonidine). [158,159] Two hours of analgesia for labor was reported from either 100 or 200 micro gram intrathecal clonidine alone, although blood pressure decreased more with the larger dose (18% vs. 10%), and more ephedrine was required for hypotension with this dose. Combination of 100 and 200 micro gram intrathecal clonidine with 7 and 2 micro gram sufentanil, respectively, only increased duration of analgesia by another 40 min, while increasing further the incidence of hypotension. These preliminary data suggest that intrathecal clonidine doses less than 100 micro gram should be examined to diminish the risk of hypotension.

Cesarean Section (50 Patients, 40 Receiving Clonidine). [24,157] Analgesic effects of 150 micro gram intrathecal clonidine were compared with saline placebo in a double-blind trial in women after general anesthesia for cesarean section. [24] Clonidine provided pain relief for 7 plus/minus 2.2 h vs. 3 plus/minus 2.8 h compared with saline. Notable side effects included hypotension, sedation, and dry mouth, although no oxyhemoglobin desaturation, respiratory depression, or delayed hypotension or bradycardia occurred. In a similar study design and patient population, the same group investigated responses to 150-, 300-, and 450-micro gram doses of intrathecal clonidine. [157] Clonidine produced dose-dependent and long-lasting analgesia (7 plus/minus 1.3, 10 plus/minus 1.3, and 14 plus/minus 1.3 h, respectively), approaching that obtained from intrathecal morphine in this patient population. Sedation was also dose dependent and more pronounced after 450 micro gram intrathecal clonidine, although no cases of delayed sedation, hypotension, or respiratory depression were observed. Blood pressure decreased less after 300 and 450 micro gram than after 150 micro gram clonidine, consistent with a pressor effect at peripheral sites. These preliminary data suggest that prolonged analgesia after cesarean section is possible with intrathecal clonidine, although sedation and hypotension occur. The combination of intrathecal clonidine and opioids for postcesarean section analgesia has not been examined.

Peripheral Nerve Block (440 Patients, 261 Receiving Clonidine) *RF 160-168*

Clonidine has been added to local anesthetic for brachial plexus, intercostal, and peribulbar block. For brachial plexus block, a combination of 3 studies in 190 patients receiving clonidine added to 1% mepivacaine [161,167,168] demonstrated a dose-dependent prolongation of duration of anesthesia and analgesia (Figure 6) and motor block by clonidine. Clonidine has no such effect when administered intramuscularly rather than with the local anesthetic,

suggesting a local, neural effect. [161] In doses greater than 100 micro gram, addition of clonidine results in sedation, decreased blood pressure, and heart rate, and transient oxyhemoglobin desaturation was noted in several patients during deep sedation after addition of 300 micro gram clonidine. [163] When added to 1% lidocaine for brachial plexus block, 30 and 90 micro gram clonidine intensified the block by one report, [163] but 150 micro gram clonidine had no effect on quality or duration of block in another. [160] Similarly, addition of 150 micro gram clonidine was reported to increase plasma concentrations of lidocaine after brachial plexus block, [160] but similar clonidine doses (120 and 240 micro gram) were reported to have no effect on plasma concentrations of mepivacaine for the same block. [166] Whether this represents a truly different interaction between clonidine and lidocaine compared with mepivacaine is unclear, because the experience with lidocaine is, to date, quite limited.

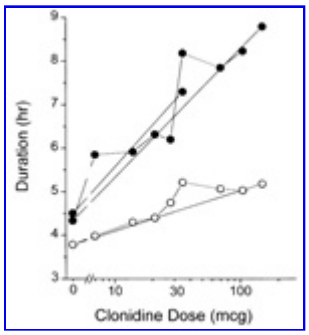


Figure 6

Clonidine also was reported to enhance other peripheral nerve blocks. Tschernko et al. [162] demonstrated less pain during and after surgery and fewer postoperative analgesic requests in patients receiving 2 micro gram/kg clonidine with bupivacaine intercostal blocks than if the same clonidine dose was given intramuscularly, and there was less oxyhemoglobin desaturation if clonidine was administered with the bupivacaine. Similarly, 100-150 micro gram clonidine prolongs akinesia, reduces the need for reinjection, and reduces dose of local anesthetic for peribulbar block. [164,165]

Summary and Recommendations

The reasonably extensive clinical experience with clonidine reflects the broader veterinary experience with alpha$_2$ -adrenergic agonists in regional anesthesia and is consistent with our knowledge of the pharmacology of these agents from the laboratory. Epidural clonidine appears to offer unique advantages over existing agents in the treatment of certain chronic pain conditions. Clonidine, added to local anesthetics for epidural, spinal, or peripheral block, prolongs and intensifies anesthesia for surgery. Postoperatively, a combination of epidural clonidine with opiates offers the advantage of reduced dose of each component with correspondingly fewer side effects. Therefore, clonidine clearly adds to existing agents for regional anesthesia in a variety of settings (Table 5).

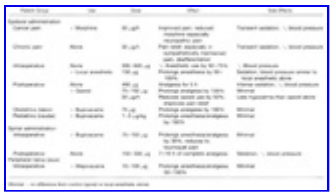


Table 5

Clonidine also produces side effects, primarily hypotension, bradycardia, and sedation. Although experience in more than 2,000 patients, most in the perioperative period, suggests clonidine is safe, blood pressure and heart rate should be monitored for at least 2 h after bolus clonidine injection and intravenous access maintained for fluid or drug administration. Sedation from clonidine is clearly dose dependent, and, whereas clonidine does not produce severe respiratory depression like opioids, sporadic reports of transient oxyhemoglobin desaturation during snoring sleep suggest that pulse oximetry should be considered if large boluses (> 300 micro gram) of clonidine are to be administered.

In summary, alpha$_2$ -adrenergic mechanisms of regional analgesia have been exploited for more than 100 years in humans. The pharmacology of clonidine suggests it will be useful in many regional anesthetic techniques, as is borne out in this initial clinical experience. Although not revolutionary, clonidine and other alpha$_2$ -adrenergic agonists will likely expand the scope and improve the reliability and efficacy of regional anesthesia.

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