

Perineural Administration of Dexmedetomidine in Combination with Bupivacaine Enhances Sensory and Motor Blockade in Sciatic Nerve Block without Inducing Neurotoxicity in Rat

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Background: **The current study was designed to test the hypothesis that high-dose dexmedetomidine added to local anesthetic would increase the duration of sensory and motor blockade in a rat model of sciatic nerve blockade without causing nerve damage.**

Methods: **Thirty-one adult Sprague-Dawley rats received bilateral sciatic nerve blocks with either 0.2 ml bupivacaine, 0.5%, and 0.5% bupivacaine plus 0.005% dexmedetomidine in the contralateral extremity, or 0.2 ml dexmedetomidine, 0.005%, and normal saline in the contralateral extremity. Sensory and motor function were assessed by a blinded investigator every 30 min until the return of normal sensory and motor function. Sciatic nerves were harvested at either 24 h or 14 days after injection and analyzed for perineural inflammation and nerve damage.**

Results: **High-dose dexmedetomidine added to bupivacaine significantly enhanced the duration of sensory and motor blockade. Dexmedetomidine alone did not cause significant motor or sensory block. All of the nerves analyzed had normal axons and myelin at 24 h and 14 days. Bupivacaine plus dexmedetomidine showed less perineural inflammation at 24 h than the bupivacaine group when compared with the saline control.**

Conclusion: **The finding that high-dose dexmedetomidine can safely improve the duration of bupivacaine-induced antinociception after sciatic nerve blockade in rats is an essential first step encouraging future studies in humans. The dose of dexmedetomidine used in this study may exceed the sedative safety threshold in humans and could cause prolonged motor blockade; therefore, future work with clinically relevant doses is necessary.**

ALTHOUGH the use of peripheral nerve catheters has increased in recent years, the majority of anesthesiologists still perform single-injection peripheral nerve blocks. Long-acting local anesthetics alone can provide excellent analgesia for up to 9–14 h.[1–4] This often leaves patients feeling their first pain during the nighttime hours, however, thereby interrupting patients' sleep on the first postoperative night. The goal for anesthesiologists then becomes finding ways to prolong the duration of single-shot regional techniques to keep patients comfortable longer.

The efficacy of clonidine, a α_2-adrenoceptor agonist, in a variety of regional anesthesia techniques has been established.[5] Clonidine has been shown in many clinical studies to prolong the duration of anesthesia and analgesia in peripheral nerve blocks, although results with long-acting local anesthetics have been somewhat less impressive.[6–15] A few studies have found no beneficial effect with the addition of clonidine.[16–18]

Dexmedetomidine (Precedex®; Hospira, Inc., Lake Forest, IL) is a selective α_2-adrenoceptor agonist approved by the US Food and Drug Administration for continuous intravenous sedation in the intensive care setting. A pilot study performed by our group (data not presented) showed that perineural dexmedetomidine added to 0.25% bupivacaine in rat sciatic nerve injections enhanced the duration of sensory and motor blockade. Other studies have found dexmedetomidine to be safe and effective in various neuraxial and regional anesthetics in humans, including intrathecal[19] and intravenous regional anesthesia.[20]

Studies have shown that local anesthetics cause myonecrosis; however, it is believed that the damage may not be clinically significant because the muscle normally regenerates.[21–24] Local anesthetics do not cause any direct nerve damage unless they are injected intraneurally or given in higher concentrations than that which is commercially available. Local anesthetic doses that are generally safe in healthy patients, however, may indeed be neurotoxic in patients with preexisting subclinical disease states, such as diabetes with subclinical neuropathy and multiple sclerosis.[25–27] Currently, there are no known human or animal histologic data available for dexmedetomidine injected perineurally in the periphery either by itself or in combination with a local anesthetic. This study was designed to test the hypothesis that high-dose dexmedetomidine added to a local anesthetic would improve the duration of sensory and motor blockade of sciatic nerve blocks in rats without significant nerve or tissue damage.

Materials and Methods

This study adhered to American Physiologic Society and National Institutes of Health guidelines and was approved by the University of Michigan Committee for

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the Use and Care of Animals (Ann Arbor, Michigan). All procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*‖ and the *Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research*.#

Drug Preparation

Dry bupivacaine was made up to a concentration of 1% and mixed with either normal saline or dexmedetomidine to make final concentrations of 0.5% bupivacaine and 0.5% bupivacaine plus 0.005% dexmedetomidine. In addition, 0.01% dexmedetomidine was mixed with normal saline to make 0.005% dexmedetomidine. The pH for all drugs was maintained at 5.69 ± 0.05.

Subfascial Sciatic Nerve Injection

An investigator (C.M.B.) blinded to the drug condition performed both the injections and subsequent neurobehavioral testing. Thirty-one adult male and female Sprague-Dawley rats (cesarean-derived Sprague-Dawley) weighing 250–350 g were purchased from Charles River Laboratories (Wilmington, MA). Rats without any signs of preprocedural neurobehavioral impairment were anesthetized and maintained with 1.5% isoflurane. The sciatic nerve of both hind extremities was exposed using a lateral incision over the thigh and division of the superficial fascia as previously described.[28–30] After the dissection, the sciatic nerve was clearly identified at a point proximal to its bifurcation. Under direct vision, all rats received bilateral injections of 0.2 ml total volume of drug per injection into the perineural space below the clear fascia covering the nerve and proximal to the bifurcation of the sciatic nerve. Sixteen rats in the bupivacaine–dexmedetomidine (Bupiv-DMET) group received either 0.5% bupivacaine (0.2 ml) or 0.5% bupivacaine plus 0.005% dexmedetomidine (0.2 ml) assigned at random, with the other drug injected on the contralateral side. Fifteen rats in the saline–dexmedetomidine (Saline-DMET) group received either 0.005% dexmedetomidine (0.2 ml) or normal saline (0.2 ml) assigned at random, with the other drug injected on the contralateral side. Injections were made using a tuberculin syringe and a 30-gauge needle. A nonabsorbable muscle fascia suture was placed at the midpoint of the injection site as a marker for subsequent nerve removal. The suture was placed in the muscle fascia of the biceps femoris below the subcutaneous tissue and was neither directly touching nor surrounding the nerve. The incisions were closed, and isoflurane was discontinued.

Neurobehavioral Examination

Sensory processing was evaluated in paw withdrawal response to forceps pinch of the lateral foot/toe. The pinch was limited to a maximum of 1 s to avoid direct paw tissue trauma. The sciatic nerve block used did not compromise the motor nerves to the hip muscles, and the rats were, therefore, able to withdraw the tested paw in response to pain.[31,32] Sensory responses were evaluated by the withdrawal reflex or vocalization to pinch and quantified as 0 = vigorous paw withdrawal to pinch (normal sensory function), 1 = moderate withdrawal, 2 = minimal withdrawal, or 3 = full sensory block/no response to pinch.[28–30] Motor function was also assessed using the 0–3 scale. Motor function was quantified as 0 = normal motor function, 1 = normal dorsiflexion ability and the rat walking with curled toes, 2 = moderate dorsiflexion ability and the rat walking with curled toes, or 3 = no dorsiflexion ability and the rat walking with curled toes.[31,32] Sensory and motor function were evaluated every 30 min until the complete resolution of blockade.

Histopathologic Evaluation

After the neurobehavioral examination, rats were assigned to one of two groups for sciatic nerve removal and pathologic evaluation. Nerves were removed during general anesthesia at 24 h (Bupiv-DMET group, n = 14; Saline-DMET group, n = 14) or 14 days (Bupiv-DMET group, n = 18; Saline-DMET group, n = 14). Approximately 1.5 cm of nerve was removed with the injection site at the midpoint as marked by the fascial suture in the muscle directly above. To avoid any trauma-induced artifacts, care was taken not to stretch the nerves during the removal process. Nerves were placed in 2.5% glutaraldehyde for 24–72 h and then washed three times and placed in a phosphate buffer. In the Bupiv-DMET group, 24 of the 32 nerves were sent for histopathologic evaluation (n = 12 at 24 h, n = 12 at 14 days). In the Saline-DMET group, 18 of the 28 nerves were sent for evaluation (n = 10 at 24 h, n = 8 at 14 days). Those that were not analyzed were stored at 4°C after harvesting and fixation. Nerves were cut into 5-μm sections and stained with hematoxylin and eosin and Luxol fast blue.

A pathologist, blinded to experimental treatment, analyzed the slides using previously established scales for perineural inflammation (0 = no inflammation, 1 = small focal areas of mild edema and/or cellular infiltrate, 2 = locally extensive areas of moderate edema/cellular infiltrate, 3 = diffuse areas of moderate to marked edema/cellular infiltrate) and signs of nerve damage (0 = no lesions, 1 = 0–2% of the fibers with lesions in axons or myelin, 2 = 2–5% with lesions, 3 = more than 5% with lesions).[33,34]

‖ Guide for the Care and Use of Laboratory Animals. Washington D.C., National Academies Press, 1996. www.nap.edu/readingroom/books/labrats. Accessed May 5, 2008.

Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research. Washington, D.C., National Academies Press, 2003. www.national-academies.org/ilar. Accessed May 5, 2008.

Table 1. Sensory Scores for Bupivacaine and Bupivacaine plus Dexmedetomidine

	Bupivacaine				Bupivacaine + Dexmedetomidine				
Time, min	Mean ± SEM	Median	25th IQR	75th IQR	Mean ± SEM	Median	25th IQR	75th IQR	*P* Value
30	2.94 ± 0.06	3	3	3	2.63 ± 0.20	3	2	3	NS
60	2.88 ± 0.13	3	3	3	2.88 ± 0.09	3	3	3	NS
90	2.19 ± 0.31	3	1	3	2.88 ± 0.09	3	3	3	NS
120	2.00 ± 0.32	3	1	3	2.88 ± 0.09	3	3	3	0.016
150	1.44 ± 0.35	1.5	0	3	2.56 ± 0.20	3	2	3	0.006
180	1.38 ± 0.34	1.5	0	3	2.00 ± 0.33	3	0	3	NS
210	1.13 ± 0.30	1	0	2	1.75 ± 0.34	2	0	3	NS
240	0.75 ± 0.28	0	0	2	1.50 ± 0.33	2	0	3	0.012
270	0.44 ± 0.20	0	0	1	1.13 ± 0.30	1	0	2	0.005
300	0.19 ± 0.10	0	0	0	0.63 ± 0.22	0	0	2	0.047
330	0	0	0	0	0.19 ± 0.14	0	0	0	NA
360	0	0	0	0	0.06 ± 0.06	0	0	0	NA
390	0	0	0	0	0	0	0	0	NA

Sensory scores (complete blockade sensory score = 3, normal sensory function = 0) were significantly improved at multiple time points when the bupivacaine plus dexmedetomidine group was compared with the bupivacaine group. Time course data for sensory testing was analyzed using a nonparametric model with ordinal logistic regression for repeated measures and generalized estimating equations.

IQR = interquartile range; NA = not applicable; NS = not significant ($P < 0.05$ deemed significant).

Statistics

Sensory and motor time-course data were analyzed using SAS 9.1.3 (SAS Institute Inc., Cary, NC) and a nonparametric model with ordinal logistic regression for repeated measures and generalized estimating equations. The duration of complete sensory and motor blockade and the time to recovery of normal sensory and motor function were analyzed using GBStat version 6.5.6 (Dynamic Microsystems, Inc., Silver Spring, MD). For the analysis of complete blockade and time to recovery of normal function, analyses were completed using repeated-measures analysis of variance followed by the Tukey–Kramer multiple comparisons test. Before performing the repeated-measures analysis of variance, Kolmogorov–Smirnov and Shapiro–Wilk W tests were used to ensure normal distribution of data. The dependent measure for these analyses was time in minutes. Histopathology scores were also analyzed using GB-STAT version 6.5.6 (Dynamic Microsystems, Inc.) and were treated as nonparametric data. Analysis was completed using Wilcoxon rank sum/Mann–Whitney U test comparing all groups with the saline control.

Results

Neurobehavioral Results

Dexmedetomidine added to bupivacaine enhanced sensory blockade when compared with bupivacaine alone at time points 120, 150, 240, 270, and 300 min (table 1 and fig. 1). Dexmedetomidine added to bupivacaine also enhanced motor blockade when compared with bupivacaine alone at time points 90, 150, 180, 210, 240, 270, and 300 min (table 2 and fig. 2). Bupivacaine and bupivacaine plus dexmedetomidine enhanced sensory blockade when compared individually with saline and dexmedetomidine at time points 30 ($P < 0.0001$), 60 ($P < 0.0001$), and 90 ($P < 0.0001$) min (fig. 1). Bupivacaine plus dexmedetomidine showed significantly prolonged motor scores at time points 30 ($P = 0.009$), 60 ($P < 0.0001$), and 90 ($P < 0.0001$) min when

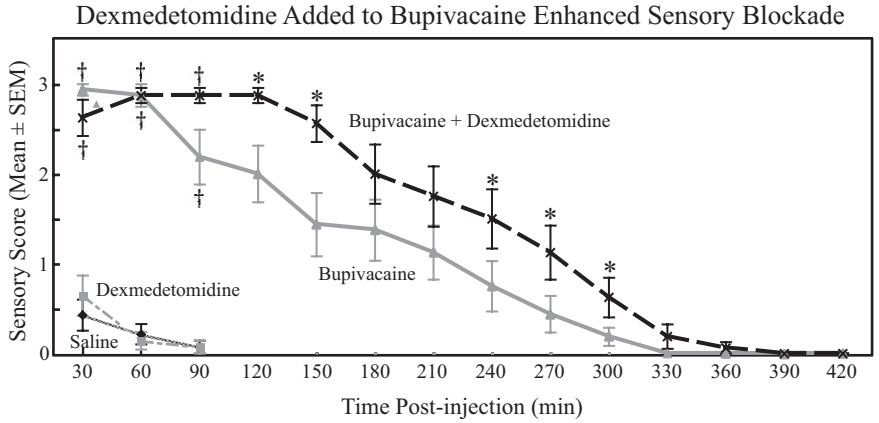

Fig. 1. Sensory blockade: Dexmedetomidine added to bupivacaine enhanced the duration of sensory blockade in response to lateral paw pinch when compared with bupivacaine alone. Bupivacaine and bupivacaine plus dexmedetomidine showed improved sensory scores when compared with saline and dexmedetomidine. The time course demonstrates the progression from complete sensory blockade (score = 3) to recovery of normal sensory function (score = 0). Time course data for sensory testing were analyzed using a nonparametric model with ordinal logistic regression for repeated measures and generalized estimating equations. * Significant differences for bupivacaine plus dexmedetomidine *versus* bupivacaine alone at specific times after injection. † Significant differences between dexmedetomidine and saline when compared with bupivacaine plus dexmedetomidine and bupivacaine.

Table 2. Motor Scores for Bupivacaine and Bupivacaine plus Dexmedetomidine

	Bupivacaine				Bupivacaine + Dexmedetomidine				
Time, min	Mean ± SEM	Median	25th IQR	75th IQR	Mean ± SEM	Median	25th IQR	75th IQR	*P* Value
30	2.69 ± 0.12	3	2	3	2.94 ± 0.06	3	3	3	NS
60	2.63 ± 0.15	3	2	3	2.94 ± 0.06	3	3	3	NS
90	2.31 ± 0.28	3	1	3	2.94 ± 0.06	3	3	3	0.042
120	2.06 ± 0.32	3	0	3	2.75 ± 0.11	3	2	3	NS
150	1.56 ± 0.32	2	0	3	2.56 ± 0.16	3	2	3	0.002
180	1.31 ± 0.30	1.5	0	2	2.19 ± 0.19	2	2	3	0.01
210	0.94 ± 0.28	0.5	0	2	1.75 ± 0.27	2	1	3	0.01
240	0.81 ± 0.28	0	0	2	1.31 ± 0.27	1	0	2	0.029
270	0.56 ± 0.24	0	0	1	1.00 ± 0.26	1	0	2	0.042
300	0.25 ± 0.11	0	0	0	0.63 ± 0.20	0	0	1	0.038
330	0	0	0	0	0.13 ± 0.09	0	0	0	NA
360	0	0	0	0	0.13 ± 0.09	0	0	0	NA
390	0	0	0	0	0.06 ± 0.06	0	0	0	NA
420	0	0	0	0	0	0	0	0	NA

Motor scores (complete blockade motor score = 3, normal motor function = 0) were significantly improved at multiple time points when the bupivacaine plus dexmedetomidine group was compared with the bupivacaine group. Time course data for motor testing was analyzed using a nonparametric model with ordinal logistic regression for repeated measures and generalized estimating equations.

IQR = interquartile range; NA = not applicable; NS = not significant ($P < 0.05$ deemed significant).

compared with saline and dexmedetomidine (fig. 2). Bupivacaine showed significantly lengthened motor scores at time points 60 ($P < 0.0001$) and 90 ($P = 0.0002$) min when compared with saline and dexmedetomidine (fig. 2).

The duration of complete sensory blockade (sensory score = 3) was significantly increased when bupivacaine plus dexmedetomidine was compared with bupivacaine. None of the rats in the Saline-DMET group ever had a complete sensory block. In addition, the time to recovery of normal sensory function (sensory score = 0) was increased when bupivacaine plus dexmedetomidine was compared with bupivacaine, dexmedetomidine, and saline (fig. 3).

The duration of complete motor blockade (motor score = 3) was significantly lengthened when bupivacaine plus dexmedetomidine and bupivacaine were individually compared with dexmedetomidine and saline. The trend toward prolonged complete motor blockade when bupivacaine plus dexmedetomidine was compared with bupivacaine was not significant. The time to complete recovery of normal motor function (motor score = 0) was significantly longer when bupivacaine plus dexmedetomidine was compared with bupivacaine, dexmedetomidine, and saline. The increased time to motor recovery was also significant when bupivacaine was compared with dexmedetomidine and saline (fig. 4).

In the Saline-DMET group, one rat was eliminated because of direct nerve damage during the dissection and was subsequently excluded and killed. All other animals underwent full neurobehavioral monitoring and subsequent nerve removal as described above in the Neurobehavioral Examination section of the Materials and Methods.

Histopathology

Sciatic nerve histopathology at 24 h and 14 days showed normal axons and myelin in all nerves analyzed

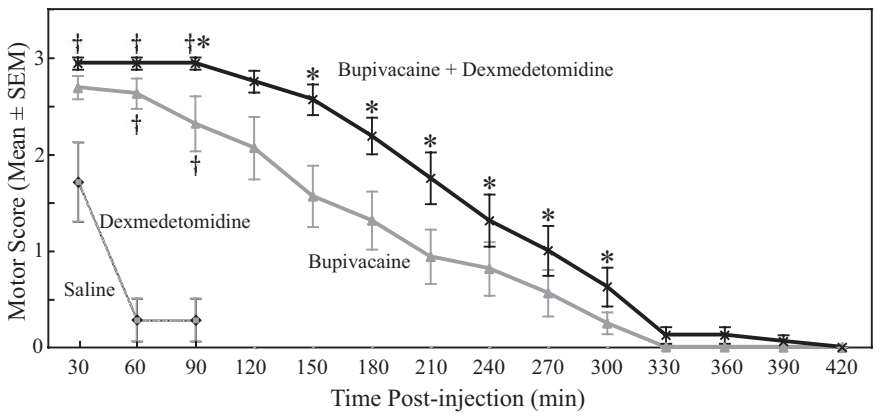

Fig. 2. Motor blockade: Dexmedetomidine added to bupivacaine also extended the duration of motor blockade over time when compared with bupivacaine alone. Bupivacaine and bupivacaine plus dexmedetomidine showed improved motor scores when compared with saline and dexmedetomidine. The time course again shows the progression from complete motor blockade (score = 3) to the return of normal motor function (score = 0). Time course data for motor testing were analyzed using a nonparametric model with ordinal logistic regression for repeated measures and generalized estimating equations. * Significant differences for bupivacaine plus dexmedetomidine *versus* bupivacaine alone at specific times postinjection. † Significant differences between dexmedetomidine and saline when compared with bupivacaine plus dexmedetomidine and bupivacaine.

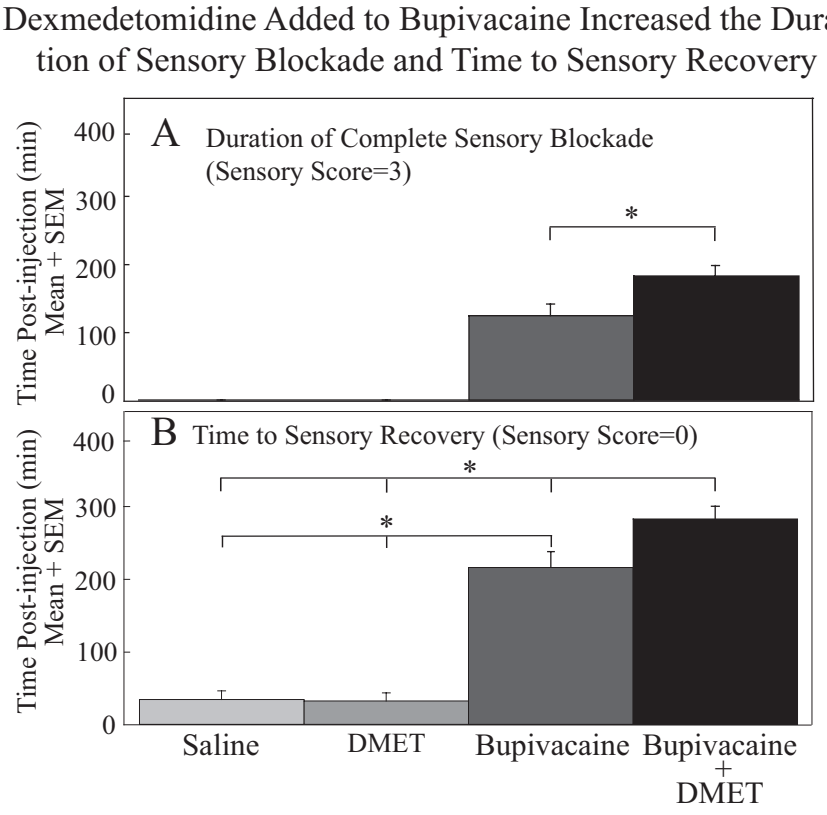

Fig. 3. The duration of complete sensory blockade (*A*) was significantly increased when bupivacaine plus dexmedetomidine (DMET) (182.0 ± 15.6 min) was compared with bupivacaine (123.8 ± 17.3 min; $P < 0.01$). None of the rats in the saline or dexmedetomidine groups had a complete sensory blockade. In addition, the time to recovery of normal sensory function (*B*) was increased when bupivacaine plus dexmedetomidine (282.0 ± 17.8 min) was compared with bupivacaine (215.6 ± 21.6 min; $P < 0.05$), dexmedetomidine (32.1 ± 11.1 min; $P < 0.01$), and saline (34.3 ± 11.7 min; $P < 0.01$). * Significant differences. Analyses were completed using repeated-measures analysis of variance followed by Tukey-Kramer multiple comparisons test. The dependent measure for these analyses was time in minutes.

(histopathology score = 0). Figure 5 shows representative sciatic nerve histopathology. When compared with the saline control group, the bupivacaine group had significantly higher perineural inflammation scores at 24 h. Nerves in the bupivacaine plus dexmedetomidine group showed less perineural inflammation at 24 h when compared with the bupivacaine group (table 3). There were no differences in perineural inflammation between the saline control, dexmedetomidine, and bupivacaine plus dexmedetomidine groups at 24 h (table 3). None of the nerves analyzed at 14 days showed significant perineural inflammation.

Discussion

Dexmedetomidine Enhancement of Sensory and Motor Blockade

In this placebo-controlled, randomized, blinded study, high-dose dexmedetomidine added to bupivacaine significantly enhanced sensory and motor blockade in sciatic nerve blocks in rats (figs. 1–4 and tables 1 and 2). The effect of dexmedetomidine was only significant when added to bupivacaine, thereby refuting the central analgesic effects of dexmedetomidine as the reason for increased duration of sensory blockade.

Dexmedetomidine alone did not produce significant sensory blockade or sustained motor blockade, which is consistent with that which has been seen with clonidine in both laboratory and clinical work. In rabbit sciatic nerves, supraclinical doses of clonidine were found to inhibit C-fiber action potentials; however, doses almost 1,000-fold lower prolonged the duration of lidocaine blocks.[35] In humans, clonidine did not provide adequate analgesia when used as the sole anesthetic in brachial plexus blockade.[36] These data along with the laboratory and clinical clonidine data suggest a possible class effect for α_2-adrenoceptor agonists in peripheral nerve blocks.

There have been four proposed mechanisms for the action of clonidine in peripheral nerve blocks. These mechanisms include centrally mediated analgesia, α_{2B}-adrenoceptor–mediated vasoconstrictive effects, attenuation of the inflammatory response, and direct action on the peripheral nerve.

Central analgesia, vasoconstriction, and antiinflammatory properties do not fully explain the efficacy of clonidine in peripheral nerve blocks. The duration of anesthesia and analgesia was prolonged with perineural clonidine compared with subcutaneous[14] and intramuscular controls.[9,37] Despite higher plasma levels of clonidine with intramuscular administration, perineural administration provided better analgesia, thereby refuting a central mechanism.[9] Although α_{2B} adrenoceptors do mediate vasoconstriction in the periphery, the vasoconstrictive properties of clonidine are weaker than those of epinephrine.[18] Unlike epinephrine, the enhancement of sensory blockade with clonidine is not attenuated by the coadministration of α-adrenoceptor antagonists.[38,39] Recent work by Eisenach *et al.* has

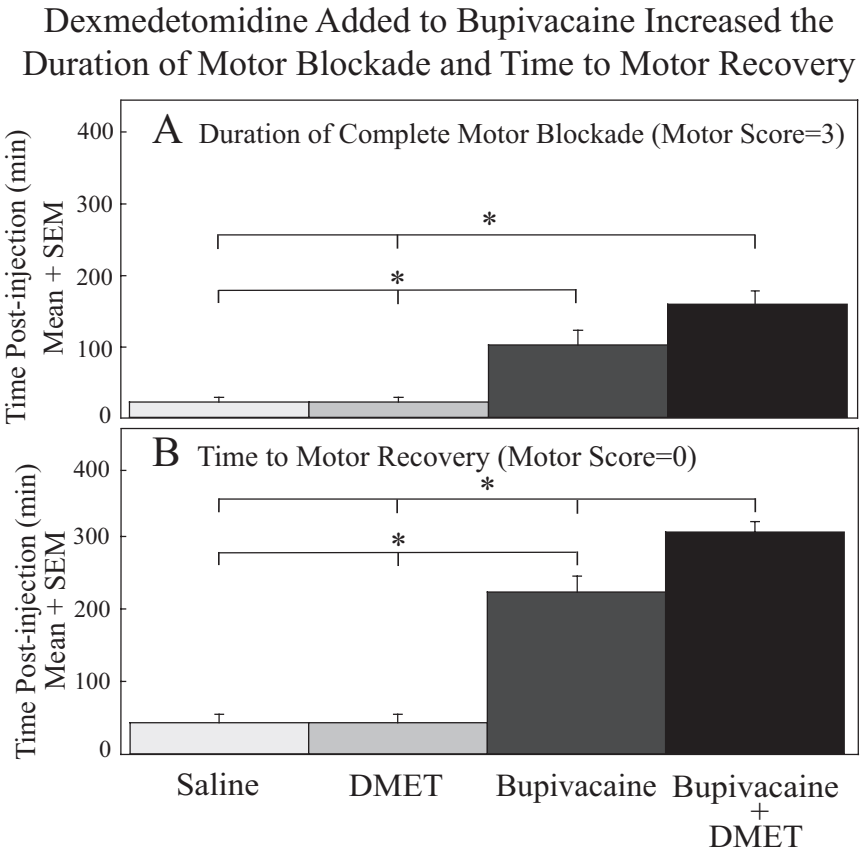

Fig. 4. The duration of complete motor blockade (*A*) was significantly improved when bupivacaine plus dexmedetomidine (DMET) (158.0 ± 19.1 min) and bupivacaine (101.3 ± 20.7 min) were individually compared with dexmedetomidine (21.4 ± 6.6 min; $P < 0.01$) and saline (21.4 ± 6.6 min; $P < 0.01$). The trend toward prolonged complete motor blockade when bupivacaine plus dexmedetomidine was compared with bupivacaine was not significant. The time to complete recovery of normal motor function (*B*) was significantly longer when bupivacaine plus dexmedetomidine (306.0 ± 14.4 min) was compared with bupivacaine (223.1 ± 22.4 min; $P < 0.01$), dexmedetomidine (42.9 ± 11.6 min; $P < 0.01$), and saline (42.9 ± 11.6 min; $P < 0.01$). The increased time to motor recovery was also significant when bupivacaine alone was compared with dexmedetomidine ($P < 0.01$) and saline ($P < 0.01$). * Significant differences. Analyses were completed using repeated-measures analysis of variance followed by Tukey-Kramer multiple comparisons test. The dependent measure for these analyses was time in minutes.

shown that α_2-adrenoceptor agonists attenuate the inflammatory response in a nerve injury model in rats.[40–45] Although these findings are extremely important in the study of neuropathic pain, they do not explain the immediate antinociceptive benefits of perineural clonidine added to local anesthetic in an acute pain model.

Laboratory work dating back as early as 1972 indicates that clonidine has a direct effect on the peripheral nerve

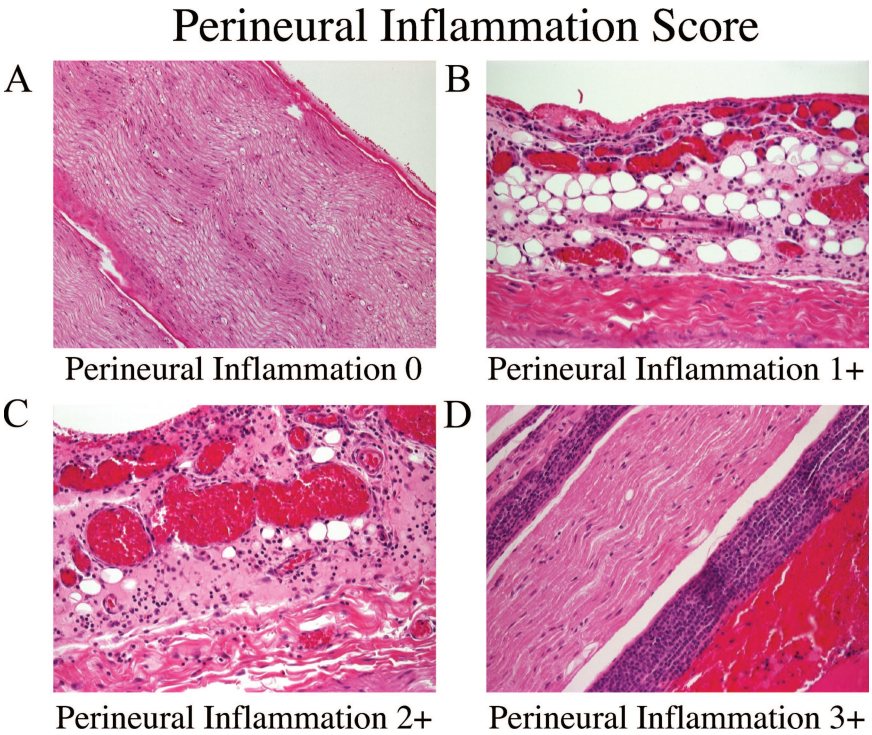

Fig. 5. Nerves were sectioned and stained with hematoxylin and eosin to assess perineural inflammation at 24 h and 14 days. Nerves in the bupivacaine group had higher inflammation scores at 24 h when compared with the saline control. Bupivacaine plus dexmedetomidine and dexmedetomidine alone had similar inflammation scores compared with normal saline at 24 h. At 14 days, nerves in both groups were completely normal with inflammation scores of 0. (*A*) Inflammation score = 0: The perineural space is void of any significant inflammatory cells. (*B*) Inflammation score = 1: Focal portions of perineural inflammation involving 5–10% of the sections. (*C*) Inflammation score = 2: Moderate degree of perineural inflammation. (*D*) Inflammation score = 3: Severe inflammation is seen with large numbers of lymphocytes surrounding the nerve.

Table 3. Histopathologic Perineural Inflammation Scores at 24 Hours

Drug	Perineural Inflammation Score			Comparison with Saline, *P* Value	Bupivacaine *vs.* Bupivacaine + Dexmedetomidine, *P* Value
	Median	25th IQR	75th IQR		
Saline	2	1	2	NA	NA
Dexmedetomidine	1	0.5	2.5	NS	NA
Bupivacaine	3	2	3	< 0.04*	< 0.04†
Bupivacaine + dexmedetomidine	1	1	2	NS	NA

Dexmedetomidine attenuated the acute bupivacaine-induced perineural inflammation. When compared with the saline control group, bupivacaine showed higher inflammation scores at 24 h. The increased perineural inflammation at 24 h when bupivacaine was compared with bupivacaine plus dexmedetomidine was also statistically significant. There were no differences between the saline control, dexmedetomidine, and bupivacaine plus dexmedetomidine groups. Perineural inflammation scores were assessed by a blinded pathologist as follows: 0 = no inflammation, 1 = small focal areas of mild edema and/or cellular infiltrate, 2 = locally extensive areas of moderate edema/cellular infiltrate, 3 = diffuse areas of moderate to marked edema/cellular infiltrate.

* Statistical significance determined based on comparison with saline placebo group (Wilcoxon rank sum/Mann–Whitney U test). † Statistical significance when bupivacaine was compared with bupivacaine plus dexmedetomidine (Wilcoxon rank sum/Mann–Whitney U test).

IQR = interquartile range; NA = not applicable; NS = not significant ($P < 0.05$ deemed significant).

that is not mediated *via* the α_2 adrenoceptor.[46] Clonidine produced a concentration-dependent, reversible blockade of compound action potentials in frog sciatic nerves,[46] rat sciatic nerves,[47] and desheathed rabbit vagus nerves.[35,48] The effects were found to be greater on C fibers than Aα fibers.[47] These local anesthetic effects at high concentrations, however, do not explain the apparent additive or synergistic effects of clonidine added to local anesthetics in peripheral nerve blocks in humans. In 1994, Gaumann *et al.*[48] exhibited clonidine's ability to increase the hyperpolarizing afterpotential that follows a single compound action potential. Kroin *et al.*[38] later found that lidocaine added to ZD 7288, a specific blocker of the I_h current, extended sensory blockade to pinprick in rat sciatic nerve blocks equivalent to the prolongation seen with the lidocaine and clonidine mixture. Dalle *et al.*[49] later corroborated this finding in a sucrose-gap method on the C fibers of rabbit vagus nerves. The authors concluded that clonidine enhances activity-dependent hyperpolarization by inhibiting the I_h current. The I_h current plays a key role in cell excitability, especially the firing frequency, in both the central and peripheral nervous systems.[50] The I_h current is activated during the hyperpolarization phase of an action potential and normally acts to reset a nerve for subsequent action potentials. Therefore, by blocking the I_h current, clonidine enhances hyperpolarization and inhibits subsequent action potentials.

There are some recent studies investigating the mechanism of action of dexmedetomidine in the central nervous system. Dexmedetomidine was found to inhibit rat hypothalamic paraventricular nucleus neurons by activation of the G protein–coupled inwardly rectifying K^+ current and paraventricular nucleus parvocellular neurons by suppression of I_h.[51] An *in vitro* study of rat dorsal root ganglion neurons found that when combined with lidocaine, both clonidine and dexmedetomidine produced an additive blockade-type interaction on tetrodotoxin-resistant sodium current.[52] Although these studies investigated central mechanisms of action for dexmedetomidine, when combined with the aforementioned clonidine literature, hypotheses as to possible mechanisms of action for dexmedetomidine in peripheral nerves can be drawn.

The current study does not elucidate the mechanism by which dexmedetomidine enhances local anesthetics in peripheral nerve blocks. It is, however, the first study to report the peripheral perineural administration of dexmedetomidine. Given that dexmedetomidine and clonidine are both selective α_2-adrenoceptor agonists, it is possible that they work in a similar manner and may indicate a class effect. The peripheral mechanism of clonidine, however, does not seem to be α_2 mediated.

Histopathologic Evaluation of Perineural Dexmedetomidine

To our knowledge, this is also the first reported histopathologic evaluation of peripheral perineural administration of dexmedetomidine. Clonidine has long been used in clinical practice for oral, intravenous, subcutaneous, perineural, epidural, and intravenous administration without ill effect. In addition, previous studies of intrathecal administration of high doses of clonidine in rats[53] and dogs[54] did not find any toxicity to the spinal cord or nerve roots. A study published while the current results were being reviewed found demyelinization of the oligodendrocytes in the white matter of the spinal cord when dexmedetomidine 5 or 10 μg was injected into the epidural space in rabbits.[55] The rabbits in the higher-dose epidural dexmedetomidine group received between 6.06 and 6.25 μg/kg, and the spinal cords were removed for histopathologic analysis 60 min after drug injection and only 1 day after the placement of the epidural catheter. A saline group was not included, and the injectate pH was neither adjusted nor reported. The neurotoxic effects of epidural dexmedetomidine reported could be due to a species effect, pH, vasoconstriction of the spinal cord vascular supply, or direct trauma from epidural placement.

In the current study, all of the nerves analyzed for histopathologic changes were normal at 24 h and 14 days. The concentration of dexmedetomidine was based on our proposed human clinical dosing of 2 μg/kg for peripheral nerve blocks. This concentration was derived from previous human epidural and intravenous regional anesthesia studies. Estimating the average patient to be 75 kg, the concentration for a 30-ml brachial plexus block would be 5 μg/ml. Therefore, the current study used a concentration of 50 μg/ml for a total dosing between 28 and 40 μg/kg to demonstrate a wider safety margin for both concentration and total dosing. Although there are significant differences between epidural and peripheral perineural administration, it is surprising that the 28–40 μg/kg used in the current study did not affect the axons or myelin of the sciatic nerve, whereas the 6.25 μg/kg in the epidural rabbit model led to significant myelin damage.[55] Future studies in other animal species may help to clarify this discrepancy.

Consistent with the previously noted decrease in inflammatory mediators after perineural clonidine administration,[40–45] the current study found a significant reduction in perineural inflammation at 24 h when dexmedetomidine was added to bupivacaine as compared with bupivacaine alone. Bupivacaine alone had higher perineural inflammation scores at 24 h compared with the saline control group (table 3). Both the bupivacaine plus dexmedetomidine and dexmedetomidine alone groups showed perineural inflammation scores similar to the saline control group. As previously discussed, the decrease in perineural inflammation is believed to be due to a decrease in proinflammatory products from immune cells recruited to the site of injury and an increase in antiinflammatory cytokines.[40–45]

Local anesthetics are known to be myotoxic[21–24]; however, the clinical significance of local anesthetic–induced myotoxicity is still somewhat unclear because there are few reported cases of significant muscle pathology in the literature. This study did not investigate the myotoxic effects of local anesthetics combined with dexmedetomidine and may be an area of future research. Although the reports of clinically significant myotoxicity are limited to date,[23] as regional anesthesia grows, the number of reported cases would be expected to increase. In addition, the increased use of peripheral nerve catheters[56–58] and infusion over several days may make this issue more significant. As previously noted, some patients may be at a higher risk of postprocedural neurologic dysfunction due to comorbidities, such as diabetes or multiple sclerosis.[25–27] In these patients, the proinflammatory, neurotoxic effects of local anesthetics may be contraindicated. The ability of α_2-adrenoceptor agonists to attenuate the inflammatory response[40–45,56] may improve safety in peripheral nerve catheters and single-shot blocks.

Limitations

As noted above, the concentration of dexmedetomidine used far exceeds that which we propose as a potentially appropriate human dose, and the effects of more clinically relevant doses in this species are still unknown. In addition, it is unknown whether human responses to clinically relevant doses would be significant.

Clonidine is known to produce a dose-dependent inhibition of Aα and C fibers, with C fibers having been shown to be more profoundly affected.[35,47,48] C fibers are known to mediate dull pain and burning sensations; however, the model used for neurobehavioral monitoring in the current study was equivalent to a surgical stimulus. Although dexmedetomidine added to bupivacaine was shown to enhance both sensory and motor blockade, using a model to elicit dull pain may have shown more subtle sensory differences. This difference may better correlate with the postoperative sensory changes previously seen in human perineural clonidine studies.[6–15]

In addition, rats received high doses of dexmedetomidine, which is known to cause sedation. Whereas high doses, between 28 and 40 μg/kg, were necessary to prove a satisfactory safety margin, the neurobehavioral monitoring was likely altered. Systemic dexmedetomidine is known to provide analgesia and sedation, which might also affect sensory and motor testing. Each rat received bilateral sciatic nerve blocks, however, and thereby acted as its own control. Furthermore, a blinded investigator conducted the neurobehavioral testing. Rats in the Saline-DMET group never had a complete sensory block, nor was their motor block as sustained as that which was seen in the Bupiv-DMET group. Although rats in the Saline-DMET group did have short durations of complete motor blockade, this was likely a product of centrally mediated sedation. However, the motor blockade seen in the Saline-DMET group was far less consistent than that in the Bupiv-DMET group and tended to remit quickly. Using a model in which separate rats received unilateral, single blocks with local anesthetic plus dexmedetomidine *versus* local anesthetic alone may be interesting. It would, however, be very difficult to blind because of the sedative effects of high-dose dexmedetomidine. Future dose ranging studies will help to determine whether clinically relevant doses may have the same effect.

Conclusions

This study supports the hypothesis that large-dose dexmedetomidine enhances the duration of bupivacaine anesthesia and analgesia of sciatic nerve block in rat. The results are consistent with laboratory clonidine data. The histopathologic evaluation showed that nerve axon and

myelin were normal in both groups at 24 h and 14 days. To our knowledge, this is the first study to evaluate nerve histopathologic changes of a high-dose α_2-adrenoceptor agonist in peripheral nerve block in rats. Under the conditions of the study, high-dose dexmedetomidine attenuates the acute bupivacaine-induced perineural inflammation without causing nerve damage. The finding that dexmedetomidine can safely improve the duration of bupivacaine-induced antinociception after sciatic nerve blockade in rats is an essential first step encouraging future studies in patients.

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