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Analgesic and sympatholytic effects of low-dose intrathecal clonidine compared with bupivacaine: a dose–response study in female volunteers

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Editor's key points

- Intrathecal clonidine has been used to improve the quality of analgesia.
- There is limited knowledge of analgesic effects of clonidine at doses below 100 μg.
- This volunteer study examined thermal sensory responses to determine dose–response effects of clonidine.
- A dose–response was demonstrated with analgesic effects at doses above 25 μg of intrathecal clonidine.
- This study provides further information on dose selection for intrathecal clonidine.

Background. A wide range of doses has been suggested for intrathecal clonidine, but no dose-ranging study has examined analgesic effects below 100 μg. The primary aim of this volunteer study was to assess the dose *vs* analgesic effect relationship for doses of intrathecal clonidine below 100 μg.

Methods. After IRB approval and signed informed consent, 11 healthy female volunteers participated in this randomized, double-blinded, cross-over study using a dose-ranging sparse-sampling technique. Participants received intrathecal clonidine (doses 0–100 μg; $n=10$) and intrathecal bupivacaine (doses 0–8.8 mg; $n=9$) on separate study days. At baseline, 30, and 60 min from drug administration, experimental heat pain tolerance was assessed at both a lumbar and a cranial dermatome. Heat and cold perception thresholds were assessed at the same time intervals. Heart rate (HR), arterial pressure, and forearm–finger and toe-leg cutaneous temperature gradients ($T_{finger-arm}$ and $T_{toe-leg}$) were used as measures of sympatholysis.

Results. Both intrathecal clonidine and bupivacaine caused significant, dose-dependent analgesic effects at the leg but not the head. Significant analgesia to experimental heat pain was detected above 25 μg clonidine and 3 mg bupivacaine. Administration of bupivacaine but not clonidine resulted in a significant dose-related decrease in HR and $T_{toe-leg}$; neither drug caused dose-related sympatholytic effects in the doses used.

Conclusions. After 50 μg clonidine or 5 mg bupivacaine, the heat pain tolerance increased by ∼1°C, similar to the analgesic effect of 5 mg epidural morphine or 30 μg epidural fentanyl in previous studies using this experimental heat pain model. Our results provide additional data for rational dose selection of intrathecal clonidine.

Keywords: anaesthesia, spinal; bupivacaine; clonidine; female; human volunteers; injection, intrathecal; pain threshold; sympatholytics

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Thirty years have elapsed since the first experimental data were published demonstrating the analgesic effects of neuraxial clonidine[1] and over 20 yr since the first clinical trials in acute postoperative pain[2] and intractable cancer pain.[3] While neuraxial clonidine is occasionally used as the sole analgesic drug,[4 5] it is more commonly administered as an adjuvant analgesic supplementing the effects of local anaesthetics,[6] opioids,[7 8] or both.[9 10] Clonidine administered by the epidural or intrathecal route exerts prominent analgesic actions by acting on pre- and post-synaptic α-2-adrenergic receptors in the dorsal horn.[11] However, intrathecal clonidine can also be associated with haemodynamic side-effects caused by sympatholysis.[12]

While a wide range of doses has been suggested for intrathecal administration of clonidine, no dose-ranging study has examined the analgesic effects of intrathecal clonidine for doses lower than 100 μg. Despite this, most recent clinical trials on intrathecal clonidine have administered doses below 100 μg.[13 14] The primary aim of this study was assessment of the dose *vs* analgesic effect relationship for doses

below 100 μg to provide an additional rationale for dose selection. Secondary endpoints were the effects of clonidine on sensory perception thresholds and sympatholysis. Clonidine's effects were compared with those of bupivacaine, a benchmark local anaesthetic for intrathecal administration that shares some of the haemodynamic side-effects of clonidine.

Methods

Study protocol

The Institutional Review Board of Stanford University approved the study and volunteers gave written informed consent for participation. The study was conducted in the Human Pain Laboratory at the Department of Anesthesia at Stanford University School of Medicine. Eleven volunteers were studied, of whom 10 were administered clonidine and nine were administered bupivacaine (see the Results section for explanation). Subjects were recruited by advertising in the university campus and were reimbursed for participation. All subjects were within 15% of ideal body weight as defined by the Metropolitan Life Insurance tables. All subjects had a normal medical history and examination, and had a negative pregnancy test (urinary β-human chorionic gonadotropin) immediately before each study day. All women were on a mixed oestrogen–progestogen oral contraceptive and study sessions were booked to coincide with the 20–24th days of the pill cycle. Other than oral contraceptives, no subject took prescription drugs. Over-the-counter medication was not allowed for 24 h before each study day. Study days were scheduled on two consecutive months. Before each study day, subjects fasted overnight. The study was conducted in a quiet room at an ambient temperature set at 20°C (to facilitate mild resting vasoconstriction). On arrival at the study centre, a 20 G i.v. catheter was placed in the left arm and 500 ml of saline was administered, after which the infusion was stopped. Recording of vital signs was initiated (respiratory rate, electrocardiogram, non-invasive arterial pressure, and haemoglobin oxygen saturation). Subjects were connected to temperature sensors attached to the right forearm, right index finger, right calf, and right great toe. Subjects wore light clothes (T-shirts and shorts, bare feet) and remained semi-recumbent throughout the study. Subjects rested and listened to relaxing music for 15–20 min before pain assessments at baseline and after drug administration. All subjects had been trained in test procedures before study participation.

Blinding and randomization

We designed a randomized, double-blinded, cross-over study, using a dose-ranging sparse-sampling technique. Different doses of each drug were chosen to cover the low-dose range. For clonidine, the selected doses in micrograms were 0, 3.9, 9.5, 14.8, 23.1, 30.0, 36.0, 56.2, 88.0, and 100.0. For bupivacaine, the selected doses in milligrams were 0, 0.25, 0.39, 0.61, 0.95, 1.48, 2.31, 3.60, 5.62, and 8.80.

Subjects were randomly assigned to receive one dose of intrathecal clonidine and one dose of intrathecal bupivacaine on different study days using a computer-based random number generator. The order of drug administration was randomized but balanced. Blinding was achieved using sealed, numbered, opaque envelopes. An unblinded investigator (E.T.R.) performed the spinal injections and prepared the medication but did not take any role in enrolment, randomization, or data collection. A blinded investigator (Y.G.) collected all the data

Intrathecal drug administration

Appropriate volumes ranging from 0 to 1 ml of clonidine (100 μg ml^{-1}; Duraclon, Roxane Laboratories Inc., Columbus, OH, USA) and from 0 to 1.17 ml of bupivacaine (7.5 mg ml^{-1}; Abbott Laboratories, Chicago, IL, USA) were aspirated into a 1 ml tuberculin syringe and then transferred by injection into a sterile 3 ml syringe. Subjects were placed in the sitting position and a 26 G atraumatic spinal needle was inserted into the subarachnoid space at either the L2/3 or L3/4 interspace using a midline approach. Correct placement was confirmed by observing free flow of cerebrospinal fluid (CSF). CSF was aspirated into the 3 ml syringe to a final volume of 3 ml before intrathecal drug injection, so that the same volume was administered intrathecally to each study participant irrespective of the dose of the study drug. There were no differences in baricity between clonidine and bupivacaine in this study and all doses were isobaric with respect to CSF (Supplementary Table S1). Drug was administered at a rate of ~0.5 ml s^{-1}. After drug administration, a further 1 ml of CSF was aspirated to confirm continued intrathecal placement and this volume was re-injected at the same rate as above. The time of intrathecal drug administration was recorded and referenced as time 'zero'. Subjects rested for 30 min after the intrathecal injection.

Heat pain tolerance

Heat pain tolerance was assessed at baseline and 30 and 60 min after drug administration. Heat pain tolerance rather than the heat pain threshold was assessed because it provides a better signal-to-noise ratio and is a more sensitive measure to detect drug-induced analgesic effects.[15 16] Furthermore, supra-threshold pain is likely to be clinically more relevant than pain at the threshold level.[15 16] For example, supra-threshold experimental heat pain stimuli were able to predict acute postoperative pain, but heat pain threshold was not.[17] Experimental heat pain was used as comparative data on neuraxial drug effects were available from two previous studies.[15 18]

A thermal sensory analyzer (TSA 2001, Medoc Advanced Medical Systems, Ramat Yishai, Israel), with a hand-held 16×16 mm thermode, was used to administer nociceptive heat stimuli at the antero-medial right thigh (L2) and at the right cheek (second branch of fifth cranial nerve). The algorithm to determine the heat pain tolerance (the heat stimulus that causes maximum tolerable pain) has previously