Premedication with low dose oral clonidine does not enhance postoperative analgesia of intrathecal morphine

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Purpose: A number of studies have demonstrated that perioperative intravenous, intrathecal, and epidural clonidine enhance postoperative analgesia. The results of previous studies on the usefulness of oral clonidine on enhancing postoperative analgesia have been mixed. The effect of a single preoperative dose of oral clonidine on postoperative analgesia was assessed in this study.

Methods: Forty-three male patients undergoing radical prostatectomy were randomized to receive either $3 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine or placebo *po* 90 min prior to surgery. All patients received isobaric 15 mg bupivacaine and intrathecal $5 \mu\text{g}\cdot\text{kg}^{-1}$ morphine, followed by a standardized general anesthetic, consisting of thiopental, sufentanil, rocuronium, isoflurane, oxygen and air. Postoperatively, PCA morphine use and visual analogue pain scores were recorded for the first 48 hr. The incidence and severity of side effects such as sedation, nausea, and pruritus were assessed, as well as patient satisfaction. Usage of PCA morphine was compared.

Results: There was no difference in total morphine requirements between the placebo and oral clonidine groups, nor in six hourly morphine usage ($P = 0.96$). Second, there was no difference in visual analogue pain scores, or the incidence of side effects. Patient satisfaction was high in both groups and again, no differences between groups was noted.

Conclusions: Oral clonidine $3 \mu\text{g}\cdot\text{kg}^{-1}$ as a premedication does not prolong the effect of intrathecal morphine: there was no difference in PCA morphine requirements ($P = 0.96$). Clonidine did not effect the incidence or severity of nausea or pruritus.

Objectif : Nombre d'études ont démontré que l'administration périopératoire, intraveineuse, intrathécale et péridurale de clonidine améliore l'analgésie postopératoire. Les études antérieures sur l'utilité de la clonidine orale en analgésie postopératoire ont donné des résultats variables. L'effet d'une dose préopératoire unique de clonidine orale sur l'analgésie postopératoire est évaluée dans la présente étude.

Méthode: Quarante-trois patients devant subir une prostatectomie radicale ont reçu, soit $3 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine, soit un placebo *po* 90 min avant l'opération. Tous les patients ont reçu 15 mg de bupivacaine isobare et $5 \mu\text{g}\cdot\text{kg}^{-1}$ de morphine intrathécale suivis d'une anesthésie générale normale comprenant : thiopental, sufentanil, rocuronium, isoflurane, air et oxygène. Après l'opération, l'utilisation de morphine sous forme d'ACP et les scores de douleur à l'EVA ont été enregistrés pendant les 48 premières heures. L'incidence et la sévérité des effets secondaires, comme la sédation, les nausées, le prurit ont été évalués de même que la satisfaction du patient. L'utilisation de morphine ACP a été comparée.

Résultats : Il n'y a pas eu de différence intergroupe quant à la consommation totale de morphine et à la l'utilisation horaire de morphine mesurée à six reprises ($P = 0,96$). De plus, il n'y a pas eu de différence de scores de douleur ou d'incidence d'effets secondaires. La satisfaction du patient était élevée dans les deux groupes, et encore une fois, sans différence intergroupe.

Conclusion : L'administration orale de $3 \mu\text{g}\cdot\text{kg}^{-1}$ de clonidine comme prémédication ne prolonge pas l'effet de la morphine intrathécale : il n'y a pas de différence de consommation de morphine en ACP ($P = 0,96$). La clonidine ne modifie pas l'incidence ou la sévérité des nausées ou du prurit.

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CLONIDINE is a selective α -2 agonist, and has a variety of properties that are of potential benefit when used as premedication. It reduces sympathetic activity, and produces sedation and anxiolysis. It decreases anesthetic requirements of inhalation agents, intravenous agents such as propofol, and intraoperative opioids.¹⁻³ It has been suggested that it may improve intraoperative cardiovascular stability by attenuating increases in blood pressure and heart rate, and may decrease myocardial ischemia.⁴ Oral clonidine also may be useful for premedication for regional anesthesia as it not only results in sedation, but it enhances and prolongs the effect of local anesthetic.⁵

Several studies found that perioperative intravenous,⁶ intrathecal,⁷ and epidural clonidine^{8,9,10} produce analgesia. The primary mechanism of clonidine analgesia is via a non-opioid, spinal action on α -2 receptors in the dorsal horn of the spinal cord. A few studies suggested that the use of oral clonidine may enhance postoperative analgesia but the results have been mixed.¹¹⁻¹⁵ Other investigators have suggested that oral clonidine potentiates the effect of intrathecal morphine.¹⁶ Furthermore, there is speculation on the minimal effective dose of oral clonidine which enhances postoperative analgesia,^{11,13} as well as the minimal effective dose of clonidine which enhances spinal anesthesia.¹⁷

The objective of this study was to determine if a single preoperative dose of oral clonidine improved postoperative analgesia by decreasing morphine requirements in patients undergoing major abdominal surgery who received a single dose of intrathecal morphine.

Methods

The study was approved by the local ethics committee on human investigation and written, informed consent was obtained from each patient. This investigation was a prospective double-blind, placebo-controlled study. Male patients, ASA status I - III, scheduled to undergo radical prostatectomy were selected. Exclusion criteria included patients receiving preoperative clonidine or with a history of an adverse reaction to clonidine or morphine, patients with valvular heart disease, patients with a history of considerable alcohol use, and patients receiving medication with psychotropic activity or chronic analgesic therapy. Fifty two male patients were enrolled in the study when assessed in our preadmission clinic, where the visual analogue pain scale, and the use of the PCA pump was explained. The patients were randomized by the hospital pharmacy by the use of a randomization table, to receive either 3 μ g·kg⁻¹ clonidine or placebo (vitamin C) *po*. The study medication was

administered 90 min preoperatively by the nursing staff in the same-day admission unit so that the anesthesiologist was blinded.

On arrival in the operating room, vital signs and sedation score were recorded, then an intravenous line was started and the patient was given a bolus of 500 ml Lactated Ringers solution. All patients received a spinal anesthetic at the level of the L₂₋₃ or L₃₋₄ intervertebral space with 15 mg isobaric bupivacaine (0.5%), and intrathecal 5 μ g·kg⁻¹ morphine, followed by a standardized anesthetic induction consisting of 0.5 μ g·kg⁻¹ sufentanil, 2-3 mg·kg⁻¹ thiopental until loss of consciousness, and 0.6 mg·kg⁻¹ rocuronium. Anesthesia was maintained with isoflurane, oxygen, and air, and 10-20 mg rocuronium as required for muscle relaxation. Hypotension, defined as a decrease in systolic blood pressure > 25% of the preoperative value was treated with 0.1 mg·kg⁻¹ ephedrine. Bradycardia (decrease in heart rate >25% of preoperative value or a rate < 45 bpm) was treated with 0.1 mg·kg⁻¹ atropine. The incidence of these hemodynamic intraoperative events was noted and the total dose of ephedrine was tabulated. At the end of surgery, the trachea was extubated as soon as possible after antagonism of the neuromuscular block with edrophonium and atropine.

In the postoperative recovery room, the patients were assessed by the nursing staff at frequent intervals for the occurrence of incisional pain. If pain was > VAS 4, or the patient found the pain unacceptable they received 1-2 mg morphine, every five minutes, until the PCA pump was started. The PCA settings were 1 mg·dose, lockout of eight minutes, with a four hourly maximum of 25 mg. The PCA morphine requirements were tabulated every six hours for 48 hr. The morphine received in the recovery room was included in the first PCA six hour requirement (0-6 hr). The intensity of pain was assessed using a visual analogue scale (VAS) 0-10 (0=no pain, 10=worst pain imaginable) and was measured at the time of discharge from the postanesthetic care unit at rest, and every 12 hr for 48 hr thereafter, at rest and with coughing by the nursing staff in the PACU and on the ward.

The duration and regression of spinal anesthesia was not directly assessed. The sensory level determined by sensation to ice, was determined on admission to the recovery room, as well as the duration of time to achieve the discharge criteria. Discharge criteria included: pain at a level acceptable to the patients, and/or visual analogue pain score < 5, minimal nausea, sedation score $\leq$ 2, ability to flex knees after a spinal anesthetic, blood pressure, and heart rate within normal limits for the patient, and respiratory rate of 8-24bpm.

TABLE I Patient demographics

	Placebo	Clonidine
Number of patients	19	24
Age (yr)	61.1 ± 7	62.3 ± 5
ASA Status	2	2
Weight (kg)	80.5 ± 9	83.1 ± 15
Height (cm)	176.5 ± 10	175.3 ± 8
Duration of anesthesia (min)	160.6 ± 20	154.1 ± 25
Duration in the PACU (min)	181.2 ± 106.5	141.2 ± 48.8

Values expressed as means ± standard deviations

TABLE II Severity of postoperative side effects of preoperative oral clonidine and placebo. Scale 0=none, 1=mild, 2=moderate, 3=severe. Values given as median (25-75th quantiles)

Pruritus	
Clonidine	0 (0-1)
Placebo	1 (0-1)
Nausea	
Clonidine	1 (0-1)
Placebo	1 (0-1)
Sedation	
Clonidine	0 (0-1)
Placebo	0 (0-0)

TABLE III Incidence of hypotension and bradycardia in clonidine vs placebo groups

	Placebo	Clonidine	
Incidence of hypotension (%)	13/19 (68.4)	18/24 (75)	P = 0.63
Dose of ephedrine (average)	10 ± 9.43 mg	18.81 ± 17.97 mg	P = 0.5
Incidence of bradycardia (%)	2/19 (10.5)	2/24 (8.3)	

Sedation, nausea, pruritus were recorded using a scale from 0 to 3 (0=none, 1=mild 2=moderate, 3=severe) and reassessed every 12 hr by the nursing staff. On postoperative day three, the patients were asked to evaluate their degree of satisfaction with their postoperative pain management using a five-point Likert scale (1=very disappointing, 2=poor, 3=fair, 4=good, 5=excellent). In addition, the patients were also asked to evaluate the overall incidence and severity of side effects on same 0-3 scale that the nursing staff used.

The study was designed to have a power of 80% to detect a 30% reduction in morphine usage by enrolling approximately 20 patients per group. This was based on a literature review.^{12,14} PCA morphine usage was compared with a student t test with $t=0.04$.

FIGURE 1 Cumulative postoperative PCA morphine requirements for each six hour period in both clonidine and control groups. Results are expressed as mean and standard deviation. $P = 0.96$.

Patient demographics, duration of anesthesia, and time spent in the postoperative recovery room, VAS pain scores, incidence of bradycardia, severity of side effects, and patient satisfaction were compared with descriptive statistics.

The incidence of hypotension and the average dose of ephedrine per case were compared using a Chi-squared test and Student's t test respectively.

Results

A total of 52 patients were enrolled in the preadmission clinic. Nine patients were excluded from the study, six patients did not receive the study protocol anesthetic, one had a different surgical procedure, in one patient spinal anesthesia was not technically possible, and one patient's PCA pump was erroneously discontinued after 24 hr. Patients were similar in age, weight and height and ASA status. Duration of anesthesia, and duration of time spent in the postoperative recovery room were also equivalent in both groups (Table I).

There was no difference in total morphine requirements between the control (36.18 mg ± 38.01) and clonidine (34.21 mg ± 22.34) groups, ($P = 0.96$), nor in six hourly morphine usage (Figure 1).

Visual analogue pain scores assessed at the time of discharge from the PACU (Postanesthetic Care Unit), and every 12 hr postoperatively were not different between the two groups (Figures 2 and 3). Preoperative sedation did not differ between the two groups. Median scores for preoperative sedation (± 25th-75th quantiles) were: control 0(0-1), and clonidine 0(0-1).

FIGURE 2 VAS for pain at rest in both groups at the time of discharge from the recovery room (PACU), and every 12 hr for 48 hr at rest. Results are expressed as mean and SD.

FIGURE 3 VAS for pain with coughing in both groups every 12 hr. Results are expressed as mean and SD.

The incidence of postoperative sedation, nausea, and pruritus was low and the data were pooled and median values ($\pm 25^{\text{th}}$ to 75^{th} percentiles) determined. The two groups did not differ (Table II). The median values (25^{th} - 75^{th} quantiles) of patient satisfaction with postoperative pain management was 5 (4-5) for placebo, and 4 (4-5) for clonidine treated patients. The response rate of completing the questionnaire was 81.4% (35/43).

Similar incidences of intraoperative hypotension and bradycardia were found in both groups. The apparently higher cumulative mean dose of ephedrine

FIGURE 4 Distribution of sensory level of spinal anesthesia on admission to the postoperative anesthesia care unit.

required in the clonidine-treated group $18.81 \text{ mg} \pm 17.97$ compared with control $10.0 \text{ mg} \pm 9.43$ did not achieve statistical significance ($P = 0.5$) (Table III).

The sensory level of anesthesia was assessed on arrival in the recovery room (Figure 4). The measurement was not performed on five patients (one in the control group, and four in the clonidine treated group).

Discussion

Previous studies on the usefulness of preoperative oral clonidine to reduce postoperative PCA morphine requirements have been mixed.¹¹⁻¹⁵ Contrary to Goyashi *et al.*,¹⁶ we were unable to demonstrate that oral clonidine prolongs the effect of intrathecal morphine: there was no difference in PCA morphine requirements. The use of a dose of $3 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po* did not affect the incidence or severity of side effects such as nausea, pruritus, or preoperative or postoperative sedation.

One criticism of this study is the use of a small dose of clonidine. Others have given a dose of $5 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po*.^{12,16} A review of the literature demonstrated only two dose-response studies. Segal *et al.*¹¹ had two treatment groups, a "low-dose" group which received two doses of $3 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po*, one on the night prior to surgery and one 90 min preoperatively, plus a transdermal clonidine patch, and a "high-dose" group which received two doses of $6 \mu\text{g}\cdot\text{kg}^{-1}$ clonidine *po*, plus the transdermal patch. Both doses of clonidine were equally effective in decreasing postoperative PCA morphine requirements. Mikawa *et al.*¹³

studied the effect of oral clonidine given preoperatively on postoperative pain in children undergoing minor surgery in a randomized, placebo-controlled study. The children received either placebo, 2 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine, or 4 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine. They found that 4 $\mu\text{g}\cdot\text{kg}^{-1}$ provided lower objective pain scores and resulted in reduced requirements for postoperative supplementary analgesics (diclofenac suppositories) than the other two regimens during the twelve hours after surgery.

A smaller dose of oral clonidine was chosen for our study because of reports of the effect of oral clonidine on the duration of spinal anesthesia. Ota *et al.*¹⁸ found that 150 μg clonidine *po*, given prior to tetracaine spinal anesthesia, prolonged the duration of sensory block. A follow-up study¹⁷ evaluated 75, 150, and 300 μg clonidine *po* given 60 min preoperatively. The prolongation of tetracaine was dose dependent and reached a maximal effect at 150 μg (~ 2.5 $\mu\text{g}\cdot\text{kg}^{-1}$). Furthermore, Singh *et al.*¹⁹ found that approximately 40% of patients that received 200 μg clonidine *po* prior to tetracaine spinal anesthesia experienced episodes of bradycardia and hypotension, compared with only 10% of patients in the placebo group. Therefore, we felt that by choosing a dose of 3 $\mu\text{g}\cdot\text{kg}^{-1}$ clonidine, we would achieve maximal effect of oral clonidine on spinal anesthesia and intrathecal morphine with the minimal effect on the cardiovascular system.

The exact mechanism of the interaction of oral clonidine and spinal anesthesia remains to be determined. We found a similar incidence of intraoperative hypotension and bradycardia in both groups. The apparently higher cumulative dose of ephedrine required in the clonidine-treated group, did not reach statistical significance ($P = 0.5$).

The regression of spinal anesthesia was not directly measured. We only assessed the level of the sensory block on admission to the PACU and the duration of stay in PACU. The sensory levels did not differ between groups, nor did time to discharge from PACU (Table I).

Clonidine is rapidly and almost completely absorbed after oral administration, and reaches peak plasma concentrations within 60-90 min. The oral preparation is an inexpensive medication and at the time that the study was undertaken it was the only available form of clonidine in Canada. It is highly lipid soluble and easily crosses the blood brain barrier and, therefore, may interact with alpha-adrenergic receptors at spinal and supraspinal sites within the central nervous system. We did not measure clonidine concentrations in the blood or cerebrospinal fluid. Studies using a combination of epidural clonidine and mor-

phine²⁰⁻²³ demonstrated improved postoperative analgesia, reflected by lower pain scores, and decreased need for supplemental analgesia. Co-administration of epidural morphine and clonidine (75, 150 μg) appears not only to potentiate but also to prolong the effect of epidural morphine.^{22,23} It was our hypothesis that the use of oral clonidine would result in a prolongation of the effect of intrathecal morphine. However, this study did not support the hypothesis. The only published study, by Goyagi *et al.*¹⁶ which showed a prolongation of the analgesia of intrathecal morphine by oral clonidine used 5 $\mu\text{g}\cdot\text{kg}^{-1}$ and a smaller dose of intrathecal morphine 200 μg (~ 3.5 $\mu\text{g}\cdot\text{kg}^{-1}$): no intraoperative opioids were given and all patients were female. We elected to use a lower dose of oral clonidine, 3 $\mu\text{g}\cdot\text{kg}^{-1}$, and a higher dose of intrathecal morphine (5 $\mu\text{g}\cdot\text{kg}^{-1}$), and all our patients were male. One needs to question whether this is due to the fact that this oral dose of clonidine does not produce concentrations of clonidine in the CSF to produce to analgesia. Also, one might wonder if gender differences in pharmacodynamic and pharmacokinetic behaviour that were suggested in a recent article on the emergence from propofol²⁴ could contribute to the discrepancy in results between our study and that of Goyagi's *et al.*¹⁶

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