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Intrathecal Clonidine as a Sole Analgesic for Pain Relief after Cesarean Section

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In a small number of studies and isolated case reports, intrathecally administered clonidine has been reported to relieve intractable cancer pain and to prolong spinal anesthesia induced by various local anesthetics. A double-blind placebo-controlled clinical trial was carried out in order to evaluate the effect of intrathecal clonidine on pain following cesarean section. Twenty patients who underwent elective cesarean section received, 45 min after general anesthesia, either 150 μg (n = 10) clonidine or saline (control group, n = 10) intrathecally. Pain scores were lower in clonidine- than saline-treated patients from 20 to 120 min after intrathecal injection, as measured by a visual pain linear analog scale ($P < 0.05$). Pain relief, in terms of the first supplemental analgesic request by patients, lasted 414 ± 128 min after intrathecal clonidine and 181 ± 169 min (mean ± SD) ($P < 0.01$) after saline. Clonidine decreased systolic, diastolic, and mean arterial pressures compared to baseline values ($P < 0.05$), but heart rate and central venous pressure were unaffected (difference not significant). Maximal reduction of systolic arterial pressure was 15 ± 9%, of diastolic arterial pressure 22 ± 12%, and of mean arterial pressure 18 ± 12%. Clonidine did not affect arterial hemoglobin oxygen saturation or Pa_{CO_2}. Patients in the clonidine group were significantly more sedated ($P < 0.05$) and more frequently reported a dry mouth ($P < 0.01$) compared to the normal saline group. These results suggest that 150 μg intrathecal clonidine is effective in controlling pain following cesarean section but is not free of side effects such as hypotension, sedation, and dryness of mouth. (Key words: Analgesia: postoperative. Anesthesia, obstetric: cesarean section. Anesthetic techniques: intrathecal. Pain: postoperative. Sympathetic nervous system, α_2-adrenergic receptor agonists: clonidine.)

MANAGEMENT of postoperative pain with opioids is a widely used method, and a great variety of techniques for their use have been developed.[1] Pruritus, nausea, vomiting, urinary retention, activation of herpes labialis,[2] and especially late and unpredictable respiratory depression[3,4] have directed pain research toward use of nonopioid drugs free of side effects.[1,5]

Inhibition of afferent nociceptive information by mechanisms other than those acting on spinal opioid receptors has been demonstrated by Yaksh and Reddy.[6] Clonidine is an α_2-adrenergic agonist that in primates produces analgesia, which is antagonized by phentolamine and yohimbine[6,7] and is believed to be mediated by α_2-adrenoceptors, located postsynaptically in the dorsal horn of the spinal cord.[8–10]

Although mostly administered with other opioid drugs,[11–14] epidural administration of clonidine for postoperative pain control has been reported in a few clinical studies to produce analgesia. A double-blind clinical study has reported that epidural clonidine (3 μg/kg) lacks significant analgesic effects on severe postoperative pain, at least after thoracotomy.[15] The effective dose of epidural clonidine for postoperative patients is probably 300–800 μg, producing complete analgesia of 4–5 h duration.[12,14]

The safety of intrathecal clonidine in terms of pharmacologic side effects and possible tissue toxicity has been extensively evaluated in many preclinical animal studies.[6,16–20] In addition, previously published clinical studies concerning epidural or intrathecal administration of clonidine in humans have not reported any acute or delayed toxic effects.[11–16,21–23]

A small number of studies evaluating the analgesic effect of intrathecal administration of clonidine in humans have been published to date, indicating that intrathecal clonidine produces a strong analgesic effect at least in cancer patients.[23–25] Also, Bonnet *et al.* reported that clonidine prolongs tetracaine and bupivacaine spinal anesthesia.[26,27] However, hemodynamic depression and bradycardia are side effects that may limit intrathecal administration of clonidine in the clinical setting. Eisenach and Tong[28] recently described in an animal study the complex action of intrathecal α_2-agonists on hemodynamic parameters and the variety of factors upon which this action depends. The possibility that intrathecal administration of clonidine may produce the same or better analgesic effect compared to epidural administration, with fewer side effects and at lower doses, provides the rationale of evaluating intrathecal clonidine.

The present study, using a double-blind, placebo-controlled design, was performed to assess pain relief, hemodynamic, and other possibly adverse effects produced by intrathecal clonidine as a sole analgesic in patients after cesarean section.

Materials and Methods

PATIENT SELECTION

Twenty healthy parturients (ASA physical status 1) undergoing elective cesarean section and without previous labor were randomly assigned to one of the two treatment groups. Randomization was performed preoperatively using a table of random numbers, and the study design

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TABLE 1. Patient Data

	Group 1 (n = 10): Normal Saline	Group 2 (n = 10): Clonidine 150 μg
Age (yr)	31.6 ± 6.1	28.7 ± 4.7 (NS)
Weight (kg)	79.3 ± 6.8	85.6 ± 8.2 (NS)
Height (cm)	161.8 ± 3.6	161.9 ± 5.4 (NS)
Duration of surgery (min)	44.7 ± 6.7	40.7 ± 5.8 (NS)

Values are mean ± SD.
No significant differences between groups (NS).

was made double-blind using coded solutions of the same volume (3 ml). Written informed consent was obtained from each patient, and the study was approved by the Ethics Committee of the Medical Faculty of the University of Patras in accordance with the Helsinki II declaration. Patients were not included in the study if maternal systemic disease was present. The operations were performed in a similar manner (type of incision and operative steps, *i.e.*, Pfannenstiel's incision). The characteristics of the groups are described in table 1.

ANESTHESIA

After induction of anesthesia with thiopental (6 mg/kg) and paralysis with atracurium (0.3 mg/kg), the trachea was intubated and anesthesia was maintained with oxygen–nitrous oxide, supplemented with halothane not exceeding 0.5 vol%.[29] No additional analgesics or tranquilizers were administered before, during, or immediately after operation.

Intraoperatively, 1,000 ml Ringer's lactate was administered routinely. All patients received 40 ml/kg Ringer's lactate solution for the first 24 h postoperatively.

ASSESSMENT OF POSTOPERATIVE PAIN

Assessment of pain was made using a visual pain linear analog intensity scale (VPLA).[30] Each patient was presented with a 100-mm-long line and was told that the left end represented no pain and the right end represented the worst pain imaginable. Then they were asked to indicate with a mark on the line the intensity of their pain. Each pain assessment was immediately followed by a second one, with the patient asked first to cough deeply and then to make a mark on another, parallel line (VPLAC). Pain scores on the VPLA scale after cough were recorded in order to assess the influence of pain relief produced by intrathecal clonidine on early postoperative mobilization. Changes in pain intensity after each assessment[31] were estimated as changes in VPLA and VPLAC scores, as well as percentages of baseline pain intensity scores using the following equation:

$$\frac{\text{baseline pain score} - \text{pain score after intrathecal administration}}{\text{baseline pain score}} \times 100$$

Sensory level to pin prick and temperature was assessed immediately after pain score assessments.

POSTOPERATIVE ANALGESIA

Intrathecal puncture and administration of the coded test substance was performed 45 min postextubation for all patients in a double-blind fashion. Observations were started immediately prior to intrathecal injection (0 min = baseline). The coded test substance in group 1 (n = 10) was normal saline and in group 2 (n = 10) was 150 μg clonidine hydrochloride, both in the same volume (3 ml). Intrathecal injections were performed using a 23-G disposable spinal needle inserted with the patient lying in lateral position. The needle was inserted at interspace L2–L3 or L3–L4 depending on the body habitus, and correct placement of the needle tip within the subarachnoid space was confirmed by aspiration of cerebrospinal fluid before and after injection. The duration of analgesia was defined as the time elapsed until the patient made the first request for supplemental analgesia. When additional analgesia was requested, the patients received 50 mg intravenous meperidine and left the study.

POSTOPERATIVE MEASUREMENTS

Data recording was performed after the administration of the intrathecal medication during the 1st h, at 3, 6, 10, 15, 20, 30, 45, and 60 min, and then every hour up to 6 h, followed by 2-h intervals up to 12 h and then every 6 h up to 24 h.

Hemodynamic and respiratory data at baseline were also compared with the preoperative values.

Blood pressure (systolic, diastolic, and mean) was measured oscillometrically. Central venous pressure was measured through an intraoperatively inserted catheter *via* the external or internal jugular vein. Heart rate was monitored *via* the electrocardiograph.

Respiratory depression was considered present when the respiratory rate decreased below 9 breaths/minute and/or the Pa_{CO_2} increased to greater than 50 mmHg. Arterial blood gas tensions were analyzed using a Radiometer BMD microanalysis system before induction of anesthesia, before intrathecal administration (baseline), 6, 12, and 24 h after intrathecal administration.

The presence or absence of nausea, vomiting and pruritus was noted during each assessment.

Somnolence was scored at each time interval using the following scale: 1 = awake and alert; 2 = awake but drowsy, responds to verbal stimulus; 3 = drowsy, but

TABLE 2. Comparison of Postoperative (Baseline) Pain Scores and Duration of Analgesia after Intrathecal Injection Between the Two Groups

	VPLA		VPLAC		
	Baseline (mm)	Maximum Pain Relief (%)	Baseline (mm)	Maximum Pain Relief (%)	Duration of Analgesia (min)
Intrathecal saline (group 1, n = 10)	68.1 ± 20.4 (39–92)	53.6 ± 22.6 (36.4–85.0)*	77.8 ± 18.3 (49–95.5)	51.2 ± 9.2 (30.5–65.1)*	181.5 ± 168.9 (45–600)
Intrathecal clonidine (group 2, n = 10)	74.6 ± 19.5 (48–96)	97.8 ± 2.0 (95.1–100)	85.5 ± 11.0 (59–100)	85.3 ± 15.0 (36.8–95.9)	414.0 ± 127.9† (240–720)

Values are mean ± SD (range).
VPLA = visual pain linear analog scale score; VPLAC = visual pain linear analog scale score after deep cough.

Intergroup comparison of pain scores (two-way ANOVA, *$P < 0.05$).
Intergroup comparison of duration of analgesia (Kaplan-Meier analysis and log-rank test, †$P < 0.05$).

rousable, responds to physical stimulus; and 4 = unrousable, does not respond to physical stimulus.

Statistical Analysis

Data are presented as mean ± SD. Arterial blood pressures and heart rate are presented as percentages of baseline values (mean ± SD). Intragroup analysis of pain scores, hemodynamic parameters, respiratory rate, and blood gas values was performed on raw data using one-way analysis of variance (ANOVA), followed by *post hoc* tests for comparison to baseline (Dunnett's test). Comparison between groups was made using two-way ANOVA for repeated measurements and the Mann-Whitney U-test. Duration of analgesia in the two groups was compared using the Kaplan-Meier method and a log-rank test. Sedation scores between groups were compared using two-way ANOVA, and intragroup comparisons were performed using the Kruskall-Wallis test. Differences were considered significant when $P < 0.05$.

Results

Age, height, weight of the patient, and duration of surgery did not differ significantly between the two groups (table 1). The baseline pain scores and the hemodynamic and the respiratory values were not significantly different between groups (tables 2 and 3).

Onset of analgesia in the clonidine group was evident very shortly after intrathecal injection, and the first significant VPLA score in comparison to baseline was recorded at 10 min (fig. 1A).

Duration of analgesia, as determined by the time elapsed before the first supplemental analgesic request by the patients, lasted 181.5 ± 168.9 min (range 45–600 min) after intrathecal administration of normal saline, whereas in the clonidine-treated group the same period was 414.0 ± 127.9 min (range 240–720 min) ($P < 0.05$; table 2 and fig. 2). Maximum pain score reduction was recorded 90 min after intrathecal administration of clonidine (figs. 1A and 3A and table 2). Five of ten patients in this group reported a "no pain" state of variable duration (range 60–135 min). Pain scores (VPLA, VPLAC) were significantly less in clonidine- than saline-treated patients from 20 to 120 min‡ after intrathecal administration (figs. 1B and 3B).

No segmental spread of analgesia was detected.

Clonidine compared to normal saline produced significant reduction of arterial blood pressure (systolic, diastolic, and mean) but not of heart rate (figs. 4B and 4C) or of central venous pressure. Mean arterial pressure was significantly lower in the clonidine than in the normal saline group from 20 to 120 min after test substance administration (fig. 4B). In the clonidine group, mean arterial pressure was significantly less compared to the baseline value (89.7 ± 16.2 mmHg) between 60 and 360 min ($P < 0.05$), with a maximum decrease (18.2 ± 11.7%) recorded at 90 min after intrathecal administration (fig. 4A). Diastolic arterial pressure also decreased significantly after intrathecal clonidine, compared to intrathecal saline, from 15 to 120 min, while systolic arterial pressure decreased only from 90 to 120 min. Heart rate was not significantly different in the clonidine group as compared to the normal saline group (fig. 4C). Compared to baseline (77.1 ± 9.3 beats/min), clonidine did not significantly reduce heart rate (fig. 4A). No bradycardia (heart rate < 56 beats/min) was noted during the study period in the clonidine group. The decrease in central venous pressure was of analogous magnitude and parallel in time in both groups (difference not significant).

The degree of sedation was not significantly different between groups at baseline. Patients in the clonidine group were significantly more sedated compared to the normal saline group ($P < 0.05$) (fig. 5). Overall, sedation did not seem to be a problem in either group.

Dry mouth was reported by all patients (100%) in the clonidine-treated group. Only two patients reported a dry mouth before and shortly after intrathecal injection in

‡ Comparisons of pain scores and hemodynamics between clonidine and normal saline groups were performed up to 120 min (n ≥ 8 in saline group).

TABLE 3. Comparison of Arterial Blood Gas Values after Intrathecal Injection Between the Two Groups

	Preoperative		Baseline		6 h		12 h		24 h	
	C	NS	C	NS	C	NS	C	NS	C	NS
P_{O_2}	88.4 ± 8.5	89.9 ± 8.6	89.1 ± 6.9	91.7 ± 7.0	81.4 ± 8.0	83.3 ± 9.0	85.7 ± 6.5	84.4 ± 6.4	90.4 ± 8.8	91.4 ± 9.2
P_{CO_2}	31.4 ± 5.0	30.3 ± 5.3	30.8 ± 4.8	29.7 ± 5.2	35.3 ± 5.4	34.5 ± 5.0	35.3 ± 4.8	34.8 ± 5.0	37.6 ± 5.9	38.3 ± 5.6
*p*H	7.43 ± 0.05	7.44 ± 0.06	7.42 ± 0.05	7.41 ± 0.05	7.43 ± 0.05	7.44 ± 0.04	7.43 ± 0.05	7.43 ± 0.04	7.43 ± 0.05	7.43 ± 0.05
BE	−1.6 ± 0.6	−1.8 ± 0.7	−2.5 ± 0.6	−3.0 ± 0.7	−0.6 ± 0.6	−0.7 ± 0.7	−0.6 ± 0.7	−0.5 ± 0.6	0.7 ± 0.7	0.9 ± 0.7

Values are mean ± SD. No significant differences between groups. C = clonidine; NS = normal saline.

the control group (20%) ($P < 0.01$). Approximately 24–36 h after intrathecal injection, four patients (40%) in the clonidine and one patient (10%) in the control group reported intermittent occipital headache and pain at the posterior cervical spine region, disappearing completely over 18–24 h, without any intervention (difference not significant). Because of this occurrence, all patients in both groups were under close surveillance prior to discharge and were reevaluated periodically for a 3-month period as outpatients. During this observation period, no recurrence was noted.

Discussion

To date, only a few reports have been published evaluating the effects of intrathecal clonidine. To the best of our knowledge, this is the first double-blind, placebo-controlled clinical trial on intrathecal administration of a single dose of clonidine as a sole analgesic, documenting the benefit of its use for controlling postoperative pain after a standard surgical intervention (*i.e.*, cesarean section).

Analgesic Effects

The effective dose range of intrathecal clonidine for postoperative analgesia is not known to date. The current study suggests that compared to placebo, a single dose of 150 μg clonidine injected intrathecally produces a strong analgesic effect with a median duration of approximately 6 h. Furthermore, our patients were not administered any additional opioids,[32,33] tranquilizers, or local anesthetics[26,27,34] *perioperatively* that may have potentiated the analgesic effect of clonidine.

Preliminary clinical evaluation of a dose of 150 μg intrathecal clonidine has been found, at our institution, to induce sufficient analgesia after abdominal hysterectomy.[35] Coombs *et al.*§ suggested that neither 100 μg intrathecal clonidine nor its combination with 100 μg intrathecal morphine significantly decreased pain intensity, as measured by serial VPLA scales after laminectomy operations, compared to intravenous patient-controlled morphine (control). However, in the same study, the combination of clonidine and morphine reduced the patient-controlled morphine requirement for at least 8 h,§ which is close to the median duration of analgesia after intrathecal clonidine found in our study.

The decision as to whether or not the intrathecal administration is preferable to the epidural administration of clonidine should be based on available data concerning the doses needed to achieve a satisfactory analgesia post-

§ Coombs DW, Jensen LB, Murphy C: Microdose intrathecal clonidine and morphine for postoperative analgesia (abstract). ANESTHESIOLOGY 67:A238, 1987.

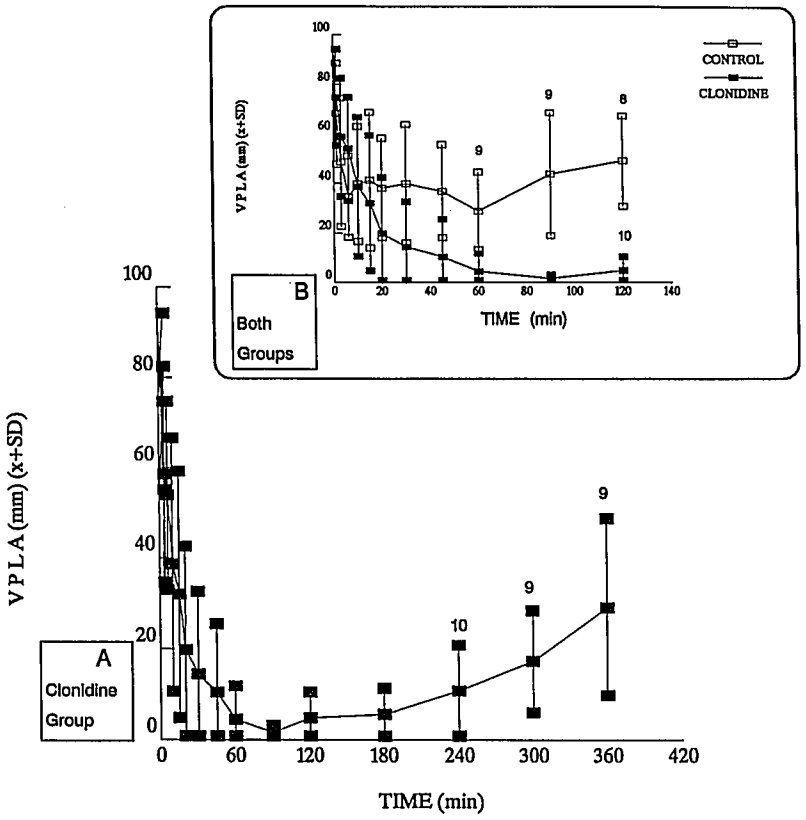

FIG. 1. Changes in pain scores (mean ± SD) until 360 min after intrathecal clonidine or normal saline. Statistics were performed by one-way ANOVA and *post hoc* Dunnett's test for comparisons to baseline (*A*). Comparisons between groups were performed by two-way ANOVA and Mann-Whitney U test up to 120 min after intrathecal injection (n > 8) (*B*). In the clonidine group, pain score was significantly lower compared to baseline from 10 to 360 min ($P < 0.01$) and significantly lower than corresponding values in the saline group from 20 to 120 min ($P < 0.05$). VPLA = visual pain linear analog scale score.

operatively as well as the side effects produced. Mendez *et al.*[14] recently confirmed the results of previous studies[12,15] concerning the effective dose range of epidural clonidine for postoperative pain relief. Their results suggested that epidural administration of clonidine (400 and 800 μg) after cesarean section produces complete analgesia of 4–5-h duration, although the authors noted that analgesia in their study may have been due, in part, to prolongation of residual epidural anesthesia. The duration and quality of pain relief following cesarean section after administration of 800 μg epidural clonidine (5 h median time to first morphine dose) and after administration of 150 μg intrathecal clonidine (6 h median time to first meperidine dose) found in our study were very close. In both studies, pain-free periods were recorded. Although different ways of pain assessment were used, comparison of these two doses suggests that they may be equipotent. Thus, it seems possible that less clonidine is needed intrathecally than epidurally to produce nearly the same analgesic effect.

Bonnet *et al.*, in two similar studies, compared the analgesic efficacy of 2 μg/kg epidural clonidine with epidural saline[36] or 2 μg/kg intramuscular clonidine[37] for pain relief after orthopedic or perineal surgery. Although the patients studied by Bonnet *et al.*[36,37] were subjected to different types of operations and were men and women, both the analgesic effects of 2 μg/kg clonidine administered epidurally and intramuscularly seem to be equivalent to the placebo effect recorded in the intrathecal normal saline group of patients in the current study. Furthermore, the epidural clonidine dose used by Bonnet *et al.* is less than the epidural dose used by Gordh (3 μg/

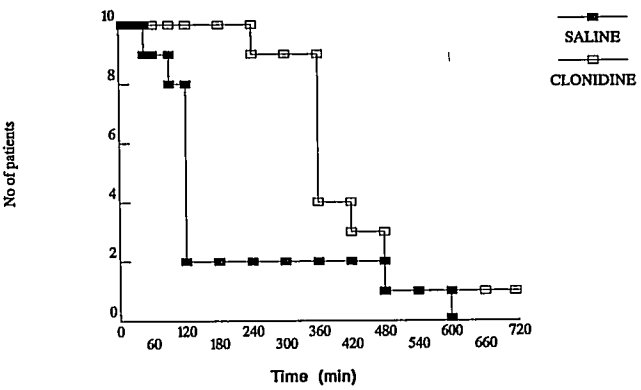

FIG. 2. Log-rank curves. Number of patients not requesting analgesia after intrathecal normal saline (filled squares) and 150 μg intrathecal clonidine (open squares). At the first request for additional analgesia, study of the individual patient was terminated. A log-rank test indicates that the two curves representing the intrathecal saline and clonidine groups are significantly different ($P < 0.01$).

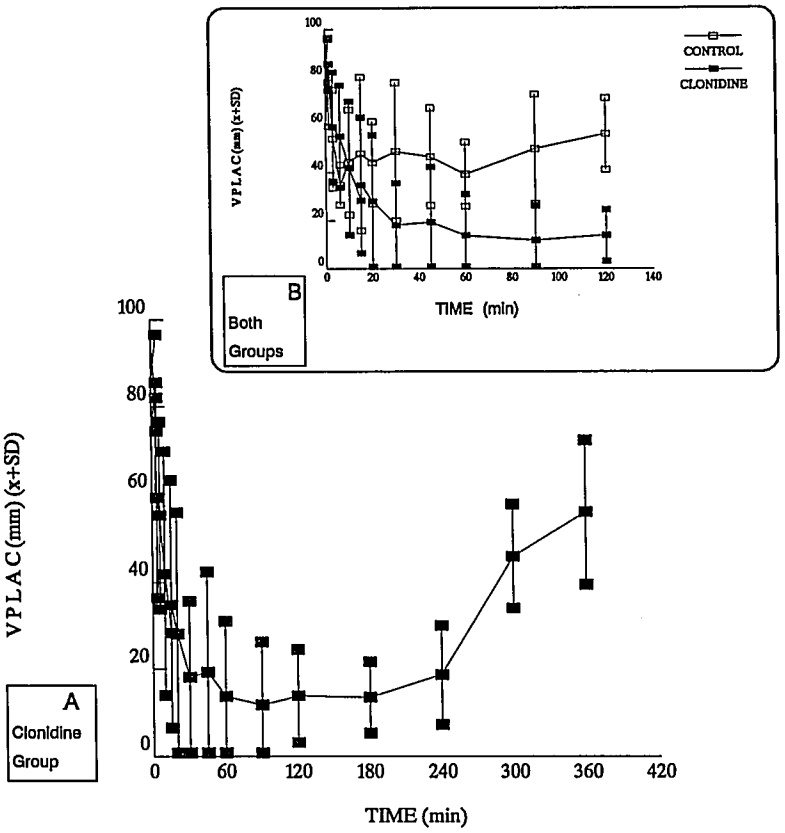

FIG. 3. Changes in pain scores assessed after cough (mean ± SD) until 360 min after intrathecal clonidine or normal saline. Statistics were performed by one-way ANOVA and *post hoc* Dunnett's test for comparisons to baseline (*A*). Comparisons between groups were performed by two-way ANOVA and Mann-Whitney U-test up to 120 min after intrathecal injection (n > 8) (*B*). In the clonidine group, pain score after cough was significantly lower compared to baseline from 6 to 360 min ($P < 0.01$) and significantly lower than the corresponding values in the saline group from 20 to 120 min ($P < 0.05$). VPLAC = visual pain linear analog scale score after deep cough.

kg),[15] who described it as ineffective, at least after thoracotomy.

HEMODYNAMIC EFFECTS

Clonidine is known to exert its hemodynamic effects by acting at several sites, either in the central nervous system or in the periphery.[7,28,38,39] Previous animal studies suggest that 1) intrathecal clonidine has a depressor effect on systemic blood pressure mediated by spinal α_2-adrenoreceptors, as well as a pressor effect and marked bradycardia, mediated by peripheral α-adrenoreceptors when a higher dose is administered[28,39]; 2) the effect of clonidine on blood pressure differs with route of administration: blood pressure decreases earlier after intrathecal than after epidural injection, corresponding with greater concentrations of clonidine in the cerebrospinal fluid[38]; and 3) only thoracic intrathecal clonidine injection (100 or 300 μg) decreases blood pressure, whereas these doses do not affect blood pressure when injected at other sites (lumbar or cervical).[28]

In humans, intermediate doses of epidural clonidine (*i.e.*, 400–600 μg) are likely to produce a greater degree of hypotension[12,14] in comparison to greater doses (700–900 μg). In contrast, other studies report that a lower epidural dose (2 μg/kg) produced significant decreases in systolic arterial pressure[15] or mean arterial pressure,[37] with a maximum decrease not exceeding 29.5 ± 11.5% of the baseline values. In the current study, hypotension was noticed shortly (20 min) after administration of clonidine as compared to saline, and the effect was more pronounced for diastolic arterial pressure.

Intrathecal clonidine (150 μg) did not produce bradycardia although a slight decrease in heart rate was noticed (difference not significant). Although in the current study a single dose of intrathecal clonidine (150 μg) was studied and our sample size was relatively small, our results suggest that this dose administered intrathecally produces hemodynamic effects similar to those produced after large doses (700–900 μg) of clonidine administered epidurally.[12]

SIDE EFFECTS

Clonidine produced drowsiness and dryness of mouth, but these effects were tolerable by the patients studied. Sedation is a common side effect when clonidine is administered and recently was demonstrated to be a dose-dependent effect.[14] In the current study, sedation was significantly more pronounced in comparison to normal saline.

In the present study, arterial blood gas tensions and

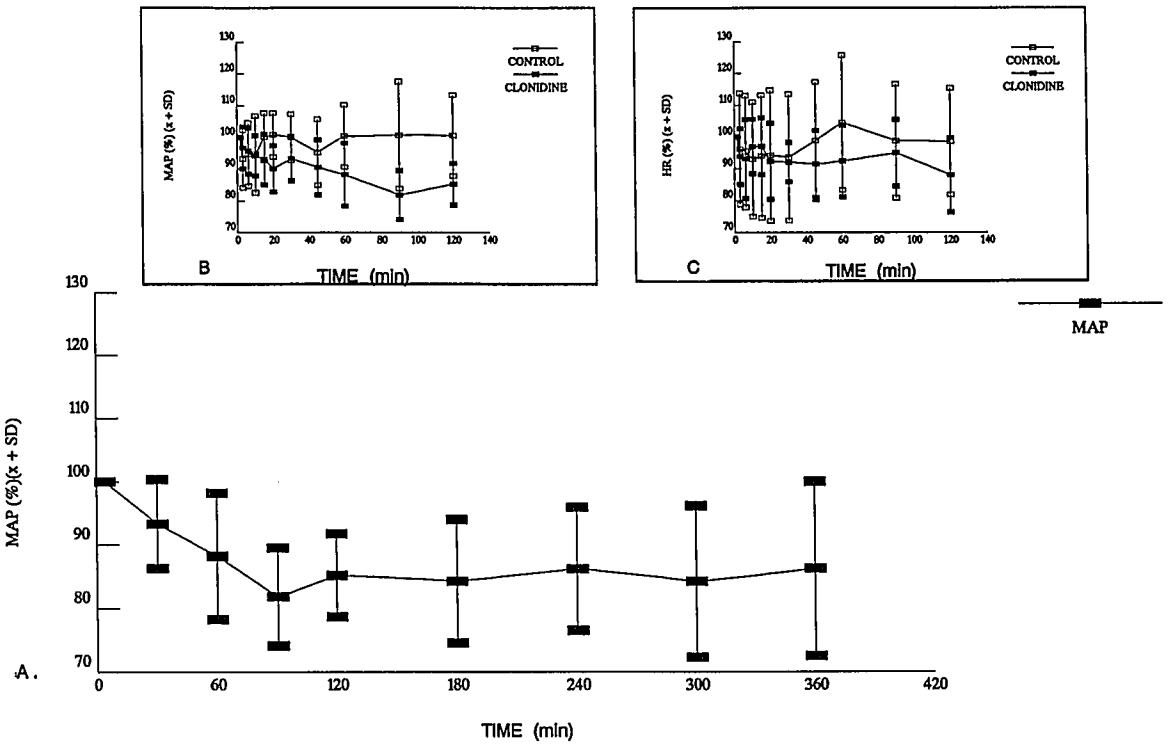

FIG. 4. Changes in mean arterial pressure (MAP) and heart rate (HR) after intrathecal clonidine or normal saline. Results are expressed in percentages (mean ± SD). In the clonidine group, MAP decreased significantly ($P < 0.05$) in comparison to baseline from 60 to 360 min (one-way ANOVA and *post hoc* Dunnett's test (*A*). Compared to normal saline group, MAP was significantly lower from 20 to 120 min ($P < 0.05$) (*B*). No significant difference was found between the groups concerning heart rate (HR) (*C*). Comparisons between groups were performed by two-way ANOVA and Mann Whitney U test up to 120 min given that fewer than eight patients remained in the study after 120 min.

respiratory rate were unaffected after intrathecal clonidine. This is in agreement with a previous study performed in healthy volunteers.[40] Nevertheless, it must be noted that the timing of arterial blood gas sampling did not correspond to the time of maximum pharmacologic effect of intrathecal clonidine.

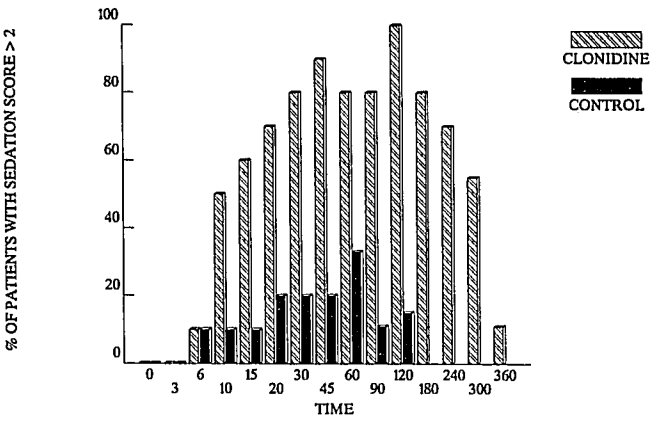

FIG. 5. Sedation, expressed as percentage of patients with sedation score ≥2 after clonidine (hatched bars) and after normal saline (solid bars) at all time points of observation period. Patients in the clonidine group were significantly more sedated compared to normal saline group (control) ($P < 0.05$). Two-way ANOVA and Kruskall-Wallis analysis were performed up to 120 min, because after that time fewer than eight patients remained in the study in the control group.

In conclusion, in this placebo-controlled study we demonstrated that 150 μg intrathecal clonidine induces effective analgesia of medium duration after cesarean section, but not without side effects such as hypotension, sedation, and dryness of mouth. We believe that before extensive clinical use of intrathecal clonidine is initiated, the following should be determined: 1) the dose range of intrathecal clonidine producing satisfactory postoperative analgesia; 2) the hemodynamic response after different doses; 3) the preferred root of administration; and 4) the preferred infusion technique (bolus *vs.* continuous).

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