Single Dose Oral Clonidine Premedication Does not Enhance Postoperative, Single Low Dose Epidural Morphine Analgesia in Hysterectomy Patients

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In this randomized, double blind placebo controlled study, the authors evaluated the effects of oral clonidine premedication on very low dose epidural morphine analgesia in 50 hysterectomy patients. Patients were randomized to receive a single oral clonidine 300 μg (n = 25) or a placebo (n = 25) 90 minutes before insertion of the epidural catheter. 3 ml of 2% lidocaine with adrenaline (5 μg ml^{-1}) mixed with 2 mg morphine were injected via epidural, followed by an additional volume of 2% lidocaine with adrenaline (5 μg ml^{-1}) titrated to T6 block height before commencing general anesthesia. The postoperative analgesia regimen was 2 mg of intravenous morphine every 10 minutes for the first 48 hr and 1 gm of oral acetaminophen every 4-6 hr after initiation of oral diet at 24-48 hr as required. Morphine consumption, acetaminophen, pain scores, and side effects were recorded thoughout 48 hr after surgery. The results show patients in the clonidine and placebo groups were not different in terms of local anesthetics dose (p = 0.27), total morphine and acetaminophen requirement (p = 0.34, p = 0.1) respectively. Pain scores at rest and movement were also not different in both groups (p = 0.83, p = 0.64) respectively. No serious adverse effects were noted. The authors concluded that oral clonidine approximately 6 μg kg^{-1} does not enhance the analgesic effect of epidural morphine 2 mg after hysterectomy.

Keywords: *Oral clonidine, Epidural morphine, Postoperative analgesia, Adverse effects, Total abdominal hysterectomy*

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Clonidine[1-3], a selective alpha-2 adrenergic agonist, has been claimed to have antinociceptive activity after intravenous[4,5] and neuraxial administration[6-9]. The adrenoreceptor system in the spinal cord plays a major role in the analgesic effect of neuraxial clonidine, however oral administration has also demonstrated this effect in equal equivalance doses. Hypotension and bradycardia after clonidine administration by inhibition of the sympathetic outflow and facilitation of the parasympathetic function in a dose-dependent manner have been reported, but were well-managed[10], however, the benefits in reducing anxiety and increasing sedation in patients undergoing surgery under regional anesthesia were of interest[11-15]. Oral clonidine enhancing effects and prolonged spinal anesthetic duration have been reported[11-12]. So oral clonidine enhancing postoperative analgesic by single dose epidural opioid, which allowed the reduction of the unwanted motor and autonomic block of local anesthetics, was introduced[16].

Results from earlier studies about the enhancement effect of oral clonidine on intrathecal and epidural morphine analgesia are contradictory and not conclusive[11-16]. This prospective, randomized, double-blind study was designed to test the hypothesis that single dose oral clonidine premedication improves postoperative analgesia by decreasing

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postoperative morphine requirements in patients undergoing total abdominal hysterectomy who receive a single bolus small dose of epidural morphine.

In addition, postoperative side effects in terms of hypotension, bradycardia and sedation were examined.

Material and Method

The study was conducted at Songklanagarind Hospital, Prince of Songkla University between May 2001 and May 2002. After approval from the Local Institutional Ethics Committee, 50 ASA I-II (American Society of Anesthesiologists physical status I or II) patients undergoing total abdominal hysterectomy were recruited. Patients were excluded if they had a history of spine deformity, had an underlying condition such as cardiovascular, renal, hepatic or neurologic disease, had a history of allergy to the drugs tested, were under current medication such as β-blockers, calcium blockers or a sedative such as benzodiazepine, or had body weight more than 20% above normal.

Patients were randomly allocated using a computer generated randomization table into clonidine and placebo groups, which were given oral clonidine 300 μg or a placebo tablet respectively, 90 min before initiation of anesthesia. Neither the patients, nurses, nor anesthesiologists caring for the patients were aware of the nature of the premedication.

Standard monitoring, namely a noninvasive blood pressure cuff, electrocardiogram and pulse oximeter were applied before the epidural catheter insertion at the L2-3 or L3-4 interspace. A pinprick test aimed to obtain the T6 block height after 13 ml of 2% lidocaine with adrenaline 5 μg ml^{-1} mixed with morphine 2 mg was administered. If the sensory block did not distribute to the T6 level, additional doses of 3 ml of 2% lidocaine with adrenaline (5 μg ml^{-1}) were given every 10 minutes. All patients received an intravenous bolus of 1 mg midazolam followed by thiopental (5 mg kg^{-1}) for induction of general anesthesia. Vecuronium was used as a muscle relaxant for intubation and maintenance, given as required. Combined anesthesia with a continuous epidural infusion of 2% lidocaine with adrenaline (5 μg ml^{-1}) at 6-10 ml h^{-1} and 67% nitrous oxide in oxygen and halothane 0.25-0.5% were conducted. Ventilation was mechanically controlled to maintain normocapnia.

Hypotension during surgery (defined as systolic blood pressure < 90 mmHg or a decrease in systolic blood pressure by more than 25% of resting value of blood pressure measured on the ward) was treated with ephedrine 6 mg intravenously repeated as necessary. Bradycardia during surgery (defined as heart rate < 45 beats/min), combined with hypotension, was treated with atropine 0.6 mg intravenously. The epidural catheter was removed on completion of surgery.

After the operation, pain intensity (the verbal rating score (VRS, 0-10)) was measured every 4 hr both at rest and during movement (from lying in bed to sitting). If the pain score at rest was greater than 5 (the highest pain score that the patient could accept), 2 mg of morphine was given intravenously, depending on the patient's demand, as frequently as every 10 minutes for the first 48 hr postoperatively. After 24 hr of surgery, when commencing the oral liquid diet, 1 gm of oral acetaminophen was given prn every 4-6 hr. The magnitudes of postoperative nausea and pruritus were assessed using a 4-point scale (0 = none, 1 = mild (no treatment required), 2 = moderate (one treatment required), and 3 = severe (more than one treatment required). If the nausea score was $\geq$ 2, patients were treated with intravenous metoclopramide 10 mg every 4 hr. The magnitude of postoperative sedation was assessed using a 4 point scale (0 = fully awake, 1 = light drowsiness, 2 = sleeping but easy to arouse, 3 = sleeping and difficult to arouse). All assessments were performed by a nursing staff member blinded to the treatment of the patient thoughout 48 hr after surgery.

Statistical analysis

The present study was designed to have a power of 80% with type I error probability of 0.05 for detection of a 40% difference in postoperative morphine consumption, as derived from a previous study[16]. There were approximately twenty-one patients required per group, and to allow for patients dropping out during the study, this number was increased to twenty-five patients per group. Unpaired-t test was used for comparison of demographic data, duration of surgery, total dose of lidocaine. Cumulative morphine requirement, pain scores, cardiovascular parameters were analyzed using repeated measured analysis of variance. Nonparametric data was analyzed using the Kruskal-Wallis analysis of variance and the Mann-Whitney U-test. Categorical data were analysed using the Chi-Square test and Fisher exact test. Results were expressed as mean $\pm$ SD. Nausea, pruritus and sedation scores were expressed as number and percentage. Statistical significance was inferred if $p < 0.05$.

Results

Twenty-five patients were enrolled in each group. One patient in the clonidine group was excluded due to accidentally receiving a higher dose of midazolam than specified in the protocol. There were no significant differences among the two groups in terms of age, weight, height, duration of surgery, duration of anesthesia, and total dose of lidocaine with adrenaline (Table 1). The mean (± SD) dose of clonidine in the clonidine group was 5.8 ± 0.9 μg kg^{-1}.

The mean (±SD) duration from the end of surgery until the first request of morphine was not significantly different between the clonidine and placebo groups (5.54±5.1 vs 6.36±5.3 h respectively; p = 0.59). The mean (± SD) doses of morphine used postoperatively were not significantly different between the clonidine and placebo groups (12 ± 7.3 vs 9.96 ± 7.5 mg; p = 0.34) (Fig. 1). The pain scores at rest and during movement determined every 4 hr until 48 hr after surgery were not significantly different between the two groups (Fig. 2, 3). The doses of acetaminophen in the placebo group tended to be less than in the clonidine group, but this did not reach statistical significance (0.96 ±1.4 vs 1.7 ± 1.6 gm, p = 0.1).

There was no significant difference of side effects including nausea, pruritus and sedation between the two groups (Table 2). Less than 10% of the patients suffered from moderate to severe pruritus and sedation.

Cardiovascular side effects were also evaluated. Perioperative blood pressure values were similar between the two groups. Heart rates immediately before induction of anesthesia and at 1, 4, and 8 h after surgery in the clonidine group were significantly less than in the placebo group (p < 0.05) (Table 3). The mean (± SD) doses of ephedrine used during surgery were also similar between the clonidine and placebo groups (2.9 ± 4.90 vs 2.4 ± 4.2 mg, p = 0.7). No patients developed respiratory depression (respiratory rate < 8 breaths/min), bradycardia (heart rate < 45 beats/min), or other complications attributable to clonidine, morphine, or both.

Discussion

The authors found no differences in postoperative intravenous morphine requirements in hysterectomy patients between the single oral clonidine and the placebo groups. In addition, the time to first intravenous morphine, accumulative morphine consumption during 48 hr and pain scores at rest and during movement during 48 hr postoperatively were

Table 1. Patient demographic, surgical and anesthetic data

Group	Clonidine (n = 24)	Placebo (n = 25)
Age (year)	41.8±5.6	44.0±6.1
Weight (kg)	52.7±6.8	52.1±5.7
Height (cm)	155.0±5.6	155.0±4.2
Duration of surgery (min)	121.3±38.7	134.0±44.7
Duration of anesthesia (min)	157.7±39.7	162.2±40.9
Total dose of 2% lidocaine (ml)	25.3±6.1	27.2±6.1

Values are mean ± SD

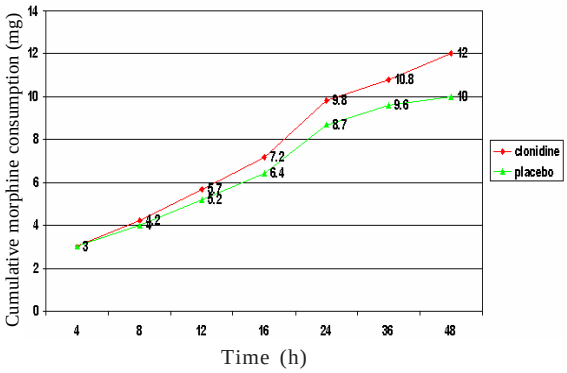

Fig. 1 Cumulative morphine consumption determined every 4 hr for the first 48 hr after surgery, p = 0.34

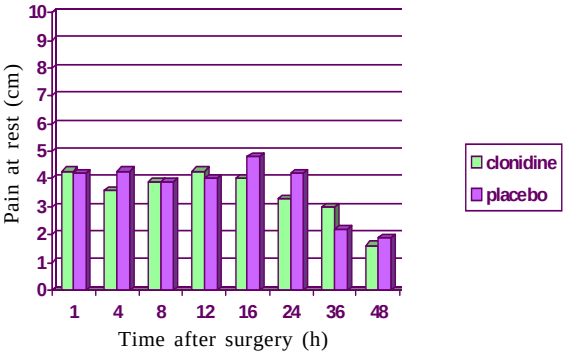

Fig. 2 Pain scores at rest 48 hr postoperatively, p = 0.70

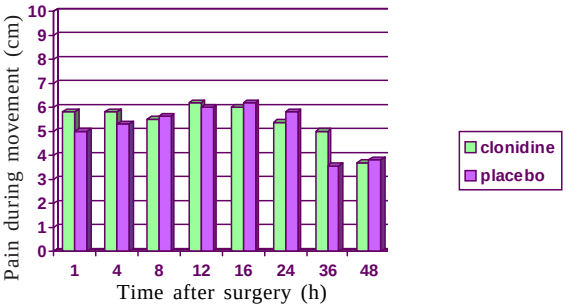

Fig. 3 Pain scores during movement 48 h postoperatively, p = 0.54

Table 2. Severity of postoperative side effects of preoperative oral clonidine and placebo

Side effects		Score 0 n (%)	1 n (%)	2 n (%)	3 n (%)	p-value
Nausea/vomiting	Clonidine (n = 24)	21 (87.5)	1 (4.2)	2 (8.3)	-	0.4
	Placebo (n = 25)	18 (72)	2 (8)	5 (20)	-	
Pruritus	Clonidine (n = 24)	18 (75)	4 (16)	2 (8.3)	-	0.63
	Placebo (n = 25)	16 (64)	7 (28)	2 (8)	-	
Sedation	Clonidine (n = 24)	17 (70.8)	6 (25)	1 (4.2)	-	0.61
	Placebo (n = 25)	17 (68)	7 (28)	1 (4)	-	

Score 0 = none, 1 = mild, 2 = moderate, 3 = severe. Values given as number and percentage (%)

Table 3. Perioperative systolic and diastolic blood pressure and heart rate

Group		Ward	Pre-induction	Hours post-surgery						
				RR	1	4	8	16	24	48
Clonidine	SBP	114±10.2	121±19.9	109±10.77	107±11.3	105±14.7	108±15.5	111±18	112±16.1	114±11.4
(n = 24)	DBP	75±7.1	72±11	67±8.6	70±8.6	68±10.6	68±10.5	72±12.5	73±9.0	78±9.2
	HR	81±5.4	78±15.3*	68±8.8*	72±9.6*	75±10.6*	78±11.4*	78±9.8	80±11.6	85±9.5
Placebo	SBP	116±12.3	129±16.5	119±16.1	111±12.4	111±14.2	111±15.5	111±13.8	117±14	111±11.6
(n = 25)	DBP	76±9.1	78±12.1	71±9.9	72±8.7	72±10.1	72±10.5	72±9.1	75±8.2	71±9.3
	HR	81±7.9	90±15.2	81±10.3	80±10.9	81±8	84±8	81±7.6	80±9.1	82±8.4

Values are mean ± SD, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR= recovery room
* Significantly different from placebo, $p < 0.05$

not significantly different in the two groups. The use of a dose of approximately 6 μg kg^{-1} of oral clonidine did not affect the incidence or severity of side effects such as nausea, pruritus and postoperative sedation.

The main reason for the negative results of the present study could be inconclusive concerning the possible antinociceptive effects of oral clonidine. Tonner et al have proposed that there may be neuropharmacological differences between oral and neuraxial clonidine, in that oral clonidine has a biphasic effect and produces antianalgesic as well as antinociceptive effects through a peripheral binding site, which is different from neuraxial clonidine that mediates analgesic as well as sedative effects at a supraspinal binding site[17]. However, factors that might be related to the biphasic effect of oral clonidine are not known. The optimum dose or analgesic dose or frequency of administration of oral clonidine, which is a factor, is still inconclusive. The single dose of clonidine used in the present study (approximately 6 μg kg^{-1}) might have resulted in an insufficient concentration to produce a stable plasma concentration through 48 hr postoperatively necessary for the enhanced effect. The heart rate values in the clonidine group due to the effect of oral clonidine were significantly lower than the placebo group only 8 hr after surgery. During 24-48 hr after surgery, the heart rate values seemed to be equal in both groups (Table 3). Thus, it is possible that the effect of 300 μg of oral clonidine preoperatively was not effective through 48 hr after surgery.

The present results support Ezri et al[14], who found that single oral clonidine 5 μg kg^{-1} premedication did not prolong the analgesia of intrathecal morphine. In addition, the study of Benhamou et al[18], even using two doses of oral clonidine 5 μg kg^{-1} preoperatively and 12 hr postoperatively, reported a negative effect from intravenous morphine. These results, however, are contrary to the study of Goyagi et al[15,16],who found that single oral clonidine 5 μg kg^{-1} enhanced the analgesic effects of intrathecal and epidural morphine. However, clonidine concentrations in the blood were not measured in these studies, or in the present study. Other authors have found that three doses of oral clonidine or two doses of oral clonidine plus a transdermal clonidine patch might result in sufficient plasma concentration to produce enhancement effect of morphine[19,20]. However, more side effects such as greater sedation and mild hypotension were also found with increased doses of clonidine. Concern about such increased side effects from the clonidine was the main reason that the authors used only a single pre-anesthetic dose.

Another possible explanation for these negative results is that the use of 2 mg of epidural morphine, which is lower than the conventional dose used in major abdominal surgery, might have been too low to be potentiated by the oral clonidine.

Significantly lower heart rate values in the clonidine group than the placebo group from pre-induction until 8 hr postoperatively were noted in the present study. This may benefit patients with pre-existing cardiovascular conditions such as myocardial ischemia[21], who require maintenance of a slower heart rate. There was no incidence of adverse side effects 48 hr postoperatively in terms of hypotension, bradycardia, or sedation.

In the present study, the authors did not control postoperative analgesic drugs except for intravenous morphine, and this may have confounded the results to some extent. The authors used oral acetaminophen to supplement postoperative analgesia combined with intravenous morphine because it is the conventional analgesic drug given after successful oral intake of clear liquids. The authors found that the morphine consumption was similar between the clonidine and placebo groups, as acetaminophen consumption 24-48 hr postoperatively tended to be higher in the clonidine group than the placebo group, but not to statistically significant levels. These results are contrary to Goyagi's study[16], which used only intravenous morphine to supplement postoperative analgesia and found significant differences in morphine consumption between the clonidine and placebo groups. The analgesic effect of acetaminophen, which is normally adequate for mild to moderate intensity pain management, and the morphine-sparing effect of acetaminophen, may have acted synergistically with the intravenous morphine and lessened the need for subsequent administration[22]. Thus, the acetaminophen consumption noted in the present study could be part of a different postoperative analgesia regimen from Goyagi's study and could be one of the reasons why morphine consumption 48 hr postoperatively was not significantly different between the two groups.

Notably, in the present study, the acceptable pain scores seemed to be higher than previous studies, perhaps due to ethnic factors. Thai patients tend to tolerate severe pain because they do not want to bother health care personnel[23].

One of the limitations in the present study may be the use of a 40% difference to detect postoperative morphine consumption, as derived from Goyagi's study[16], which may represent an overly optimistic difference. Also, the present study may have had too small a sample size (type II error) resulting in no difference in morphine consumption between the two groups.

In conclusion, in patients undergoing total abdominal hysterectomy, a single oral clonidine approximately 6 $\mu g\ kg^{-1}$ premedication did not noticeably enhance intraoperative epidural morphine 2 mg combined with a general anesthesia balanced technique, and there were no serious adverse effects.

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ยาโคลนิดีนรับประทานครั้งเดียวก่อนดมยาสลบไม่มีผลเสริมฤทธิ์การระงับปวดด้วยมอร์ฟีนในชั้นเอปิดูรัลในผู้ป่วยภายหลังตัดมดลูก

มลิวัลย์ ออฟูวงศ์, ลักษมี ชาญเวชช์, ปารมี ทองสุกใส

เพื่อศึกษาผลของยาเม็ดโคลนิดีนรับประทานก่อนดมยาสลบต่อการระงับปวดด้วยมอร์ฟีนขนาดต่ำกว่าปกติในชั้นเอปิดูรัล ผู้วิจัยจึงทำการศึกษาแบบสุ่มเปรียบเทียบในผู้ป่วย 50 รายที่มารับการตัดมดลูก โดยผู้ป่วยได้รับยาเม็ดโคลนิดีน 300 ไมโครกรัม 25 ราย และได้รับเม็ดแป้ง 25 ราย 90 นาที ก่อนเริ่มใส่สายทางเอปิดูรัล ผู้ป่วยทุกรายได้รับการระงับความรู้สึกด้วยยาชาไลโดเคนความเข้มข้น 2 เปอร์เซ็นต์ ผสมอะดรีนาลิน (5 ไมโครกรัมต่อมิลลิลิตร) ครั้งละ 3 มิลลิลิตร ร่วมกับมอร์ฟีน 2 มิลลิกรัมในชั้นเอปิดูรัล ค่อยๆเติมยาชาขนาดดังกล่าวจนระดับการชาได้ระดับทรวงอกคู่ที่ 6 แล้วจึงดมยาสลบ หลังผ่าตัดผู้ป่วยได้รับยามอร์ฟีน 2 มิลลิกรัม ฉีดทางหลอดเลือดเมื่อมีอาการปวดทุก 10 นาทีใน 48 ชั่วโมงแรกหลังผ่าตัดและเมื่อผู้ป่วยรับประทานอาหารเหลวได้ให้ยาเม็ดอะเซตะมิโนเฟนรับประทานครั้งละ 1 กรัม เมื่อมีอาการปวดทุก 4-6 ชั่วโมง ใน 24-48 ชั่วโมงหลังผ่าตัด ประเมินและบันทึกปริมาณยามอร์ฟีน, ปริมาณยาอะเซตะมิโนเฟน, คะแนนความปวดและผลข้างเคียงที่อาจเกิดขึ้นทุก 4 ชั่วโมงจนถึง 48 ชั่วโมงหลังผ่าตัด ผลการศึกษาพบว่า ไม่มีความแตกต่างของปริมาณยาชา (p = 0.27), ปริมาณยามอร์ฟีน (p = 0.34), ปริมาณยาอะเซตะมิโนเฟน (p = 0.1) คะแนนความปวดขณะอยู่นิ่ง (p = 0.83) และเคลื่อนไหวโดยลุกจากนอนเป็นนั่ง (p = 0.64) ตลอดจนผลข้างเคียงที่เกิดขึ้นระหว่าง 2 กลุ่ม ดังนั้น ยาเม็ดโคลนิดีน 300 ไมโครกรัม รับประทานก่อนดมยาสลบไม่มีผลเสริมฤทธิ์การระงับปวดด้วยมอร์ฟีน 2 มิลลิกรัมที่ให้ในชั้นเอปิดูรัล ในผู้ป่วยภายหลังตัดมดลูก