Comparison of meperidine alone with meperidine plus dexmedetomidine for postoperative patient-controlled analgesia

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ABSTRACT

الأهداف: صممت الدراسة من أجل رؤية ما إذا كان لإضافة ديكسميديتوميدين إلى ميبريدين في تسكين المرضى قد يخفف من استهلاك ميبريدين عند المقارنة مع ميبريدين لوحده.

الطريقة: تم وضع 40 مريضاً في جدول لإجراء عملية اختيارية في البطن تحت التخدير العام بمستشفى سليمان ديميرال التعليمي بمدينة اسبارتا بتركيا، في الفترة ما بين فبراير وسبتمبر 2006م. تم تقسيم المرضى عشوائياً في مجموعتين. المجموعة الأولى: تلقت ميبريدين ($0.25mg/kg^{-1}$) عبر الوريد بالإضافة الى ديكسميديتوميدين ($0.5mcg/kg^{-1}$) في (50ml) من المحلول الملحي بالانسكاب قبل انتهاء العملية الجراحية. المجموعة الثانية: وتلقت ميبريدين ($0.25mg/kg^{-1}$) عبر الوريد بالإضافة إلى (50ml) من المحلول الملحي بالانسكاب. في وحدة الرعاية لما بعد التخدير (PACU) تلقى المرضى في كلتا المجموعتين عقار ميبريدين عبر الوريد بمقدار (10mg) مع فترات فاصلة لمدة خمس دقائق حتى تصبح نقاط الألم لدى المريض أقل من نقطتين. تلقى المرضى في كلتا المجموعتين المسكنات خلال 24 ساعة بعد العملية الجراحية (ميبريدين 5mg + ديكسميديتوميدين 10mcg للمجموعة الأولى،ميبريدين 5mg للمجموعة الثانية). تم تسجيل معدل نقاط الألم ومتطلبات ميبريدين خلال فترة البقاء في وحدة الرعاية لما بعد التخدير (PACU). تم تسجيل استهلاك ميبريدين مع المسكنات حتى 24 ساعة بعد العملية الجراحية.

النتائج: كان معدل النقاط الحرفية للألم في وحدة الرعاية لما بعد التخدير (PACU) للمجموعة الأولى أقل من المجموعة الثانية ($p<0.05$). كان استهلاك ميبريدين أقل في المجموعة الثانية منه في المجموعة الأولى خلال فترة البقاء في وحدة الرعاية لما بعد التخدير (PACU) وحتى 24 ساعة بعد العملية الجراحية($p<0.01$).

خاتمة: عند المقارنة بين التسكين بعقار ميبريدين (PCA) و عقار ميبريدين بالإضافة الى ديكسميديتوميدين (PCA) تبين أن المسكن يقلل من استهلاك ميبريدين بعد العملية الجراحية.

Objectives: To investigate if the addition of dexmedetomidine to meperidine in a patient-controlled analgesia (PCA) device would reduce postoperative meperidine consumption when compared with meperidine alone.

Methods: Forty patients scheduled for elective abdominal surgery under general anesthesia in Suleyman Demirel University Medical School, Isparta, Turkey between February and September 2006, were randomly allocated into 2 groups. Group I: meperidine 0.25 mg kg^{-1} intravenous bolus and dexmedetomidine 0.5 mcg kg^{-1} in 50 ml of saline solution infusion before the end of surgery. Group II: meperidine 0.25 mg kg^{-1} intravenous bolus and 50 ml of saline solution infusion. In the postanesthesia care unit (PACU) patients in both groups received intravenous meperidine 10 mg with 5-minutes intervals until the patient's verbal pain score is lower than 2. Patients in both groups received PCA during the 24 hours after surgery (meperidine 5 mg + dexmedetomidine 10 mcg bolus for group I, meperidine 5 mg for group II). The verbal rating score of pain and meperidine requirement is recorded during PACU stay. Meperidine consumption with PCA is recorded until 24 hours postoperatively.

Results: Verbal rating score of pain in the PACU was lower in group I than group II ($p<0.05$). Meperidine consumption was lower in group I than group II during the PACU stay and until 24 hours postoperatively ($p<0.01$).

Conclusion: When compared with meperidine PCA, meperidine-dexmedetomidine PCA reduces postoperative meperidine consumption.

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Adequate postoperative analgesia is a priority. Patient-controlled analgesia (PCA) has been extensively used over recent years to titrate the analgesia need, thus avoiding the potential problems of overdose and to provide patient satisfaction with the analgesia. Dexmedetomidine is a potent α2 adrenoceptor agonist with an 8 times greater affinity for α2 adrenoceptors than clonidine.[1] The α2 adrenoceptor agonists are known to have sedative, anxiolytic, anti-shivering, analgesic, and anesthetic-sparing effects without causing respiratory depression.[2-8] Dexmedetomidine enhances the effects of analgesics without increasing the incidence of side-effects.[9,10] This observation has led to the concept that the combination of an opioid and dexmedetomidine may improve postoperative patient comfort with PCA. The major problem with dexmedetomidine may be its hemodynamic effects. Hypotension and bradycardia have been reported, particularly with more rapid infusion and in patients with pre-existing cardiac problems.[11] We chose to combine dexmedetomidine with meperidine, which has an accelerating effect on the heart rate due to its vagolytic effect.[12] The present prospective, randomized, double blind study was designed to see if the addition of dexmedetomidine to meperidine in a PCA device would reduce postoperative meperidine consumption when compared with meperidine alone.

Methods. With local research ethics committee approval, 40 patients between the ages of 21 and 56 years were recruited to a randomized double blind study in Suleyman Demirel University Medical School, Isparta, Turkey between February and September 2006. All patients were American Society of Anesthesiologists (ASA) grade I or II undergoing lower abdominal surgery under general anesthesia. Patients were excluded if there was a history of hypertension, ischemic heart disease, or conduction disturbance, a history of alcohol or drug abuse, if they were taking beta-adrenoreceptor blockers, in the case of monoamine oxidase inhibitor use within 2 weeks prior to surgery, if they had impaired hepatic or renal function or a known hypersensitivity to opioids or dexmedetomidine. Patients were given oral and written information on the study, and written consent was obtained. They were informed of the use of the PCA device at the preoperative visit. Abbott Pain Management Provider device (Chicago, IL) was used to deliver the study drugs.[13] All patients were premedicated with diazepam 10 mg 2 hours before surgery. Anesthesia was induced with thiopental 5-7 mg kg^{-1}, fentanyl 2 mcg kg^{-1}, and vecuronium 0.1 mg kg^{-1}. Anesthesia was maintained by 1-2% sevoflurane in nitrous oxide and oxygen (ratio: 40/60%). Intraoperatively, the patients were randomly allocated to 2 groups by a computer-generated table of random numbers: Patients in group I received meperidine 0.25 mg kg^{-1} as intravenous (iv) bolus and dexmedetomidine 0.5 mcg kg^{-1} in 50 ml of saline solution infused during the 10 minutes before the end of the surgery. Patients in group II received meperidine 0.25 mg kg^{-1} as iv bolus and 50 ml of saline solution infusion during the 10 minutes before the end of the surgery. Patients in both groups received PCA during the 24 hours after surgery. The PCA settings were as follows: a) meperidine 5 mg + dexmedetomidine 10 mcg bolus dose for group I, meperidine 5 mg bolus dose for Group II. b) Lockout interval of 15 minutes. c) No baseline infusion. d) No loading dose. Any color change or precipitation was not observed in the infusion bag containing the dexmedetomidine-meperidine combination. As soon as the patients were awaked in the postanesthesia care unit (PACU), their pain was assessed using a 4-point verbal rating score (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain). If the pain score was 2 or above, a recovery nurse, who was unaware of the randomization, titrated meperidine 10 mg at 5 minute intervals until the pain score was below 2. The verbal rating score of pain was recorded with 15-minute intervals and at discharge from the PACU. Total meperidine dose until the start of PCA was recorded. Once the pain score was below 2, the PCA device, containing the appropriate drug was connected to the iv access. Total meperidine consumption was assessed 3, 6, 12, and 24 hours after surgery. The patients were discharged from the PACU when their modified Aldrete score was 9 at least. The time to discharge from PACU was also recorded. After surgery, sedation was assessed on a 4-point scale (0, awake and alert; 1, drowsy; 2, mostly sleeping; 3, difficult or impossible to awaken). Sedation scores were recorded 3, 6, 12, and 24 hours after surgery. The presence of nausea and vomiting was assessed on a 4-point scale (0, no nausea or vomiting; 1, mild nausea; 2, severe nausea; 3, retching or vomiting). Patients with a nausea score of 2 or 3 were given metoclopramide 10 mg intravenously. The number of patients who vomited was recorded for each group. Mean arterial pressure, heart rate, respiratory rate, and peripheral oxygen saturation was recorded before anesthesia induction, at the extubation, at the 15th and 30th minute, and at discharge from the PACU and 3, 6, 12, and 24 hours after surgery. Blinding was carried out by an anesthetist not involved in data collection and prepared syringes containing dexmedetomidine or saline such that they appeared identical. In addition, the PCA devices containing meperidine with our without dexmedetomidine were also prepared to be seen identical by the same anesthetist. The primary end-point was defined as a reduction in meperidine consumption with PCA in the postoperative period, a 20% reduction being regarded as clinically significant.

The sample size was determined by power analysis, which revealed 20 subjects for each study group for

Table 1 - Patient characteristics and duration of anesthesia and PACU stay.

Variables	Group I n=20	Group II n=20
Gender		
Male	12	8
Female	8	12
ASA		
I	17	13
II	3	7
Age (year) (mean±SD)	46.7 ± 11.8	51.7 ± 18.9
Weight (kg) (mean±SD)	71.1 ± 9.1	73.0 ± 13.6
Duration of anesthesia (min) (mean±SD)	143.5 ± 23.2	135.3 ± 20.5
Duration of PACU stay (min) (mean±SD)	42.2 ± 11.2	38.3 ± 14.3

,PACU - Postanesthesia care unit
ASA - American Society of Anesthesiologists

Table 2 - Meperidine requirement in PACU and postoperatively (mg) (mean±SD).

Assessment time	Group I (n=20)	Group II (n=20)
PACU 15 min	11.2 ± 8.8*	22.0 ± 7.6
PACU 30 min	25.2 ± 11.7*	50.5 ± 12.3
PACU discharge	33.5 ± 16.3*	73.7 ± 23.1
3 h postoperatively (with PCA)	29.2 ± 16.2*	48.5 ± 24.7
6 h postoperatively (with PCA)	50.5 ± 23.2*	96.0 ± 41.3
12 h postoperatively (with PCA)	74.2 ± 31.7*	132.7 ± 59.3
24 h postoperatively (with PCA)	103.7 ± 44.9*	175.0 ± 77.2

PACU - Postanesthesia care unit, h - hours
*p<0.01 (Group I versus Group II)

Table 3 - Sedation scores (Median-interquartile range).

Assessment time	Group I (n=20)	Group II (n=20)
PACU 15 min	2.0 - 0*	2 - 1
PACU 30 min	2.0 - 0*	2 - 1
PACU discharge	1.5 - 1	1 - 1
3 h postoperatively	1.0 - 0*	0 - 1
6 h postoperatively	0.5 - 1	0 - 1
12 h postoperatively	0.0 - 1	0 - 1
24 h postoperatively	0.0 - 0	0 - 0

PACU - Postanesthesia care unit, h - hours
*p<0.05 (Group I versus Group II)

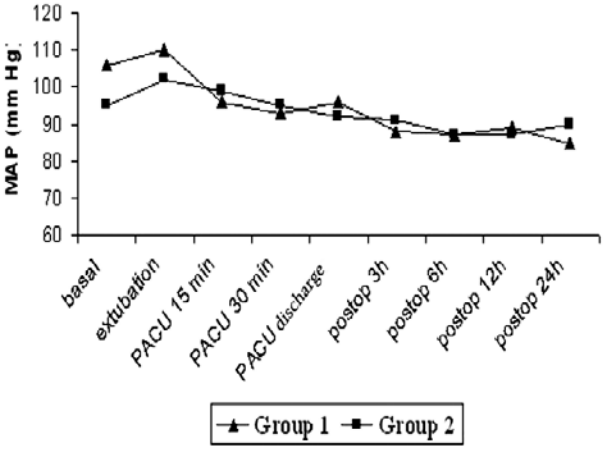

Figure 1 - Mean arterial pressure (MAP). Values are expressed as means, PACU - Postanesthesia care unit, postop - postoperative.

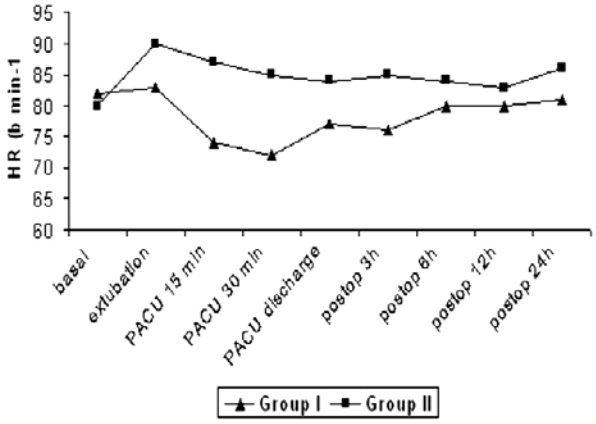

Figure 2 - Heart rate (HR). Values are expressed as means, PACU - Postanesthesia care unit, postop - postoperative.

a power of 0.8 and significance level of 0.05. The age, weight, meperidine consumption, mean arterial pressure, heart rate, respiratory rate, peripheral oxygen saturation, duration of anesthesia, and PACU stay were analyzed using Mann-Whitney U test. X-square test was used for pain and sedation score analysis, presence of vomiting and nausea, gender and ASA status of the patients. A p-value of <0.05 was considered to be statistically significant. The Statistical Package for Social Sciences software version 10.0 (SPSS Inc, Chicago, USA) was used to analyze the data.

Results. All of the 40 patients completed the study protocol and were analyzed for all the parameters. There was no difference between groups regarding gender, age, or weight and duration of anesthesia (**Table 1**). Mean arterial pressure (**Figure 1**), heart rate (**Figure 2**), respiratory rate, and peripheral oxygen saturation was similar in both groups. At the 15th minute in the PACU, verbal rating score of pain was lower in group I than group II (1.95±0.60 versus 2.45±0.76) (p<0.05). Meperidine

consumption was lower in group I than group II during the PACU stay and until 24 hours postoperatively ($p<0.01$) (**Table 2**). Sedation score during the PACU stay and at 3 hours postoperatively was higher in group I than group II ($p<0.05$) (**Table 3**). The duration of PACU stay was similar in both groups (**Table 1**). During the study period, the total number of patients experiencing postoperative nausea and vomiting was smaller in group I than group II (10 versus 20, $p<0.001$).

Discussion. Several studies showed that the combination of an opioid and an α2 agonist improves postoperative analgesia with PCA. Dexmedetomidine in combination with morphine PCA provided better analgesia for shockwave lithotripsy when compared with a tramadol/midazolam PCA combination.[14] In the study conducted by Jeffs et al,[15] the addition of clonidine to morphine, when given by PCA, improved analgesia during the first 12 hours after lower abdominal surgery. The authors suggested that this analgesic effect, which did not sustain after 12 hours following surgery might have been achieved by the clonidine loading dose alone. On the other hand, Unlugenc et al[7] found that a single iv dose of dexmedetomidine given 10 minutes before induction of anesthesia reduces postoperative patient-controlled morphine consumption during the first 24 hours. This long-lasting action may be related to the preemptive analgesic effect. As the half-life of dexmedetomidine is approximately 2 hours,[16] we chose to add dexmedetomidine to meperidine PCA with the expectation of a long-lasting decrease in meperidine consumption. With the addition of dexmedetomidine, we observed decreased meperidine need during PACU stay and until 24 hours postoperatively. Beside these studies where α2 agonists are combined with potent analgesics, Arain et al[5] compared dexmedetomidine used alone with morphine in the postoperative period. Patients receiving dexmedetomidine required 66% less morphine in the postoperative care unit when compared with the group receiving morphine. Several mechanisms have been postulated for the analgesia noted with α2 adrenergic agonists: supraspinal, ganglionic, spinal, and peripheral actions have been shown to participate in the mechanism of the analgesic effect.[8] In the CNS, among the systems modulating nociception, there are pathways using opioids and α2 adrenergic agonists.[17] Their actions are complementary and additive.[18] Although these opioid receptors and α2 agonist receptors are 2 different types of receptors, both of them may be present on the surface of the same cell. In addition, the signal transmission pathways are similar and one pathway may be shared by 2 different receptors on the same cell.[9] The anxiolytic and tymoanaleptic properties of α2 agonists may also contribute to postoperative pain control by reducing the emotional component of the pain.[14,19] In the present study, the sedative effect of dexmedetomidine, which lasted until 3 hours after surgery may have contributed to the analgesia obtained in the early postoperative period. In addition, the sedation of the patients may have caused lower use of the PCA device by the patient, which also may be regarded as a limitation of the study that would cause difficulties in interpreting the results.

In this study, the addition of dexmedetomidine to meperidine for PCA decreased postoperative nausea and vomiting in a group of patients at a high risk of experiencing this problem. It appears that dexmedetomidine may reduce postoperative nausea and vomiting. There are 2 possible explanations for this observation. First, less meperidine was used by patients who received dexmedetomidine and thereby could have reduced the risk of opioid-induced nausea and vomiting. Second, the lower incidence of postoperative nausea and vomiting may be related to the antiemetic properties of dexmedetomidine. The reduction in nausea and vomiting associated with α2 agonists has been reported previously.[3,15,20] It may be a combination of decreased norepinephrine activity and sedation that provides their antiemetic effect.[15]

A consistent effect of dexmedetomidine therapy is the development of bradycardia. Dexmedetomidine-induced bradycardia is generally related to the rapid injection of large doses of the drug.[21] In the present study, dexmedetomidine was given within 10 minutes and repeated with small PCA doses. In addition we chose to combine dexmedetomidine with meperidine, which has an accelerating effect on the heart rate due to its vagolytic effect.[12] We did not observe clinically significant bradycardia with the use of dexmedetomidine. In agreement with recent studies where dexmedetomidine has not been associated with respiratory depression,[8,22] in the present study, respiratory parameters did not differ between the groups.

As the verbal rating score of pain is a subjective measurement technique, in the present study, the consumption of analgesics by PCA device was used as an objective way to measure pain as initially described by Sechzer.[23] The efficacy of analgesics can be estimated when analgesic consumption by use of PCA is analyzed in comparable groups of patients.[24] We observed a decrease in meperidine consumption. However, this should be interpreted with caution because the observed sedation might have an effect on patients' use of PCA. Another limitation of the study is the selection of patients undergoing different types of lower abdominal surgery. It would be better to study with patients undergoing a similar type of surgery.

In conclusion, when compared with meperidine PCA, meperidine-dexmedetomidine PCA reduces postoperative meperidine consumption. Further studies

are needed to determine the optimal dexmedetomidine dose to decrease postoperative opioid consumption.

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ETHICAL APPROVAL

All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming that informed consent was obtained from each subject or subject's guardian, after receiving approval of the experimental protocol by a local human ethics committee, or institutional review board. When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed. Research papers not involving human or animal studies should also include a statement that approval/no objection for the study protocol was obtained from the institutional review board, or research ethics committee.