The Egyptian Journal of Hospital Medicine Vol., 10 : 14 – 26 March 2003
I.S.S.N: 12084
1687-2002

Epidural versus intravenous clonidine for postoperative patient controlled analgesia

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Abstract

unlike most other sedative drugs, ∝2 adrenoceptor agonists e.g (clonidine) are capable of producing both sedation and analgesia with little if any, respiratory change. The aim of this study was to evaluate the analgesic efficacy, the respiratory and the endocrine effects of epidural versus intravenous clonidine for postoperative pain. Forty adult patients ASA I and II of both sexes were scheduled for elective lower abdominal or lower extremity surgical procedures. For postoperative pain relief , the patients were randomly divided into two groups, twenty patient of each. In (Group I) patients received intravenous clonidine through patient-controlled analgesia pump (IPCA). In (Group II) patients received epidural clonidine through patient-controlled analgesia pump (EPCA).

A standard anaesthetic technique was employed to all patients and anaesthesia was maintained with gas oxygen halothane and muscle relaxant. Serial arterial and venous blood samples were taken to measure blood gases and endorphin level. After surgery patients with visual analogue scale (VAS) >4 were given clonidine initial dose 4µg/kg intravenous or epidural infusion over a period of 30 minutes then they were allowed to self administer clonidine using PCA pump which delivered a bolus dose of 0.5µg/kg with a 15 minute lockout interval to the corresponding route.

Self-administered doses were (124.2±34.637µg) in intravenous group and (100.6±31.406µg) in epidural group. The total clonidine dose was (424. ±38.138µg) in intravenous group versus (399.8±47.371µg) in epidural group. Pain scores were lower after than before clonidine administration in both groups . No significant difference in pain scores were found between the two groups. There was also no significant changes in respiratory rate, arterial PH, Pa Co2 or Pa o2 in each studied group and no significant difference between the two groups. Forced vital capacity (FVC) and Forced expiratory volume in one second (FEV1) were significantly reduced before clonidine injection in both groups. The beta endorphin level was increased after one hour of clonidine administration and there was no significant difference between the two groups. In conclusion Clonidine proves to be adequate alternative to opiates without their side effects and the dose of clonidine is lower by the epidural route.

Introduction

There is great evidence that unrelieved postoperative pain may result in harmful physiological and psychological effects and good pain relief may help to decrease postop - erative morbidity (Ready,2000). Anaesthesia and surgery are associated with dramatic decrease in functional

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residual capacity (FRC) resulting in basal atelectasis and development of pulmonary shunts (Jones et al., 1990) . Postoperative pain hinders patients from coughing effectively and co-operating in chest physiotherapy (Stoelting 1999), that may decrease the tidal volume (TV) , vital capacity (VC) and peak expiratory flow rate (PEFR). Unlike most other sedative drugs, ∝2 adreno - ceptor agonists are capable of prod - ucing both sedation and analgesia with little if any, respiratory change (Bernard et al., 1995) that makes them potentially useful in the postoperative non ambulatory settings and in intensive care situations (Hall et al.,2001) . Clonidine, a centrally acting ∝2 receptor agonist has a beneficial effect before, during and after anaesthesia such as, sedation, analgesia, increased cardiovascular stability and improved outcome (Kamibayashi and Maze, 2000) and (Fehretal., 2001).

There is currently considerable interest in attempting to combine the potent analgesic effects of drugs delivered into the epidural space with the advantage of patient participation associated with the patient-controlled-analgesia (PCA) concept. PCA system was designed whereby patients could administer their own pain relief drug and so titrate the dose to their own endpoint of adequate analgesia (Kluges 1990).

The aim of this study was to evaluate the analgesic efficacy, the respiratory and the endocrine effects of epidural versus intravenous clonidine for postoperative pain relief.

Patients and Methods

Forty adult patients ASA I and II of both sexes aged between 18-55 years admitted to Al Zahraa university hospital and were scheduled for elective lower abdominal or lower extremity surgical procedures. For postoperative pain relief , the patients were randomly divided into two groups, twenty patient of each:

Group I: Patients received intravenous clonidine through (IPCA)pump.

Group II : Patients received epidural clonidine through (EPCA)pump.

Patients who showed evidence of cardiovascular, respiratory, renal or hepatic dysfunction and patients with abnormal coagulation profile were excluded. The study protocol was explained to the patients taking their consent. Patients were instructed how to use the PCA device, and to describe the threshold of postoperative pain on the visual analogue scale (VAS).

Equipment :

Patient-controlled analgesia device : a self administered analgesic pump (Abbot life provider).

All patients in the two groups received 5mg midazolam orally at the night of operation.

Prior to induction of anaesthesia :

In group I "18" gauge cannula was placed for clonidine injection and PCA device.

In group II : a lumbar epidural technique midline approach was employed under complete aseptic conditions, where a touhy needle was inserted between lumbar level L3 – L4 or L4 – L5 interspace, position of the needle was identified by loss of resistance and an epidural catheter was introduced.

Induction was achieved by thiopentone 4-6 mg/kg and succinyl-choline 1 mg/kg and anaesthesia was maintained with 60% nitrous oxide in oxygen, halothane 0.5 –1.5 %. Muscle paralysis was achieved by atracurium 0.5mg/kg with controlled ventilation.

A 20 gauge cannula was inserted in the radial artery of the left hand of

the patients after positive Allen's test, and flushed with heparinized saline solution to allow serial measurements of arterial blood gases. Intraoperative monitoring included : ECG, non inva - sive arterial blood pressure, pulse oxi - metry and capnography, and conti - nued 24 hour after clonidine adminis - tration . No additional analgesics or tranquilizers were administered imme - diately after operation.

At the first complaint of pain, patients with VA S >4 were given clonidine (catapress) (Boehringer Inge - lheim. UK.) as 150 µg/ml in ampoules of 1 ml.

All patients received an initial loading dose of 4 µg/kg clonidine intravenous or epidural infusion over a period of 30 minute, then the patients were allowed to self administer cloni - dine using PCA pump which delive - red a blouse dose of 0.5 µg/kg with a 15 minute lockout interval to the corresponding route. Data were recor - ded at the following times :

Before clonidine administration, at 15 and 30 minutes during infusion of loading dose 4µg/kg., and at 2, 4, 6, 8, 12, 24 hours after the loading dose and during the use of PCA device.

Respiratory rate was recorded. Arterial blood gases were measured by blood gas analyzer [CHIRON Diagnostic 248 Rapid-lab] before clonidine administration, then 30 min, 4 hours and 24 hours after clonidine administration..

Pulmonary function tests were done by Respirometer (Jaeger flowmate). Forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were measured preoperative, postoperative during pain, 12hr and 24hr after clonidine administration.

Any side effects were observed and treated as follow : hypotension was treated by i.v. fluids or 3 mg ephedrine i.v. Bradycardia was treated by 0.5 – 1 mg atropine i.v.Inadequate analgesia : if the patient required analgesia in addition to self-administered doses of clonidine.

Sampling : Blood samples were taken to measure plasma level of beta-endorphin. Samples time was recorded before administration of clonidine and 1 hour after the first dose of clonidine. Blood was collected in tubes containing EDTA and Trasylol (5000 Kiu trasylol in 10 ml vacutainer tube). The samples were cooled in an ice-bath immediately, and centrifuged at 4°c. The plasma should be frozen within one hour and stored at - 20°c until assay. Beta endo - rphin in sample was extracted using Sep-Pak C 18 cartridges. The extracts were analysed by competitive radio immunoassay using antibody against synthetic human B-endorphin.

B-endorphin in standards and samples compete with 125 I labelled B-endorphin in binding to the antib - odies. 125 I B-endorphin binds to the antibodies in a reverse proportion to concentration of B-endorphin in stand - ards and samples. Antibody bound 125 I B-endorphin was separated from the fraction using the double antibody polyethylen glycol precipitation techn – ique, the radioactivity of the precipitates was measured. (Kits supplied from Gama trade company)

Statistical analysis :

All variables were expressed as mean ± SD. Comparison of patients within the same group were evaluated by using non-parametric Wilcoxon Signed-rank test. Paired simple t-test was used for comparison between groups. P-value of less than 0.05 denote a significant difference.

Results:

Demographic data were comp - arable for age, weight, height and sex as shown in table (1).

There were no significant differences between the two groups.

The initial dose of clonidine was identical in both groups (301.2±37. 480µg) in the intravenous group and (299.2±36.374µg) in the epidural group. But, the clonidine dose given via the PCA device to achieve a comparable pain relief level was lower in epidural group.

Self-administered dose were (124.2±34.637µg) in intravenous group and (100.6±31.406µg) in epidural group.

The total clonidine dose was (424. ±38.138µg) in intravenous group versus (399.8±47.371µg) in epidural group (table 2)

VAS before clonidine injection showed no significant difference in both groups (table 3).

Pain scores were lower after than before clonidine administration in both groups with no significant difference between the two groups (Figure 1).

Presence of pain in the posto - perative period have been expected to induce an alteration in pulmonary functions. Respiratory rate was unchanged throughout the study for both groups. Analgesia did not result in significant changes in respiratory rate (table 4). There was also no significant change in arterial PH, Pa Co2 or Pa o2 in each studied group throughout the observation time and no significance between the two groups (table 5), but FVC and FEV, were significantly reduced before injection of clonidine in both groups compared to baseline (preoperative) spirometric parameters (Figures 3&4).Eight hours post-injection, there were significant impro - vement in pulmonary function tests but this improvement was still low than the baseline values till the end of the study (table 6)(Figures 3&4). There were no statistical significant differences in pulmonary function tests between both groups (table 6) (Figures 3&4).

As regards, beta endorphin, both groups showed increase in plasma concentration of beta-endorphin after one hour of clonidine administration. There was no significant difference between both groups table (7) Figures(4).

Table 1 : Demographic data. Values are represented as mean ± SD. There are no significant differences between the two groups.

	Group 1 (IPCA) N= 20	Group1 (EPCA) N = 20
Age (yr) Weight (kg) Height (cm) Sex (M/F	32.2±10.30 59.0±9.46 163.4±10.11 9/11	29.4±8.70 65.8±10.06 165±9.50 12/8

Table 2 :Doses of clonidine in both groups values are represented as mean± SD.

- P value < 0.05 between groups.

	Group I		**Group II**	
	Mean	**±SD**	**Mean**	**±SD**
Initial dose Self-administered dose Total dose	**301.2** 124.2 425.4	**±37.480** ±34.637 ±38.138	**299.2** 100.6 399.8	**±36.374** ±31.406 ±57.371*

Table 3 : Visual analogue scale (VAS). Values are represented as mean ± SD. There are no significant differences between groups.

time	Group I (IPCAA)		Group II(EPCA)	
	Mean	**SD**	**Mean**	**SD**
Before	8.6	**±0.94**	8.2	**±0.82**
15min	3.3	±0.75	3.3	±0.97
30min	2.5	±0.60	2.2	±0.71
2hr	2.6	±0.55	1.8	±0.48
4 hr	2.9	±0.68	1.9	±0.68
6hr	2.25	±0.76	2.1	±0.76
8hr	2.7	±0.44	2.4	±1.31
12hr	2.1	±0.58	2.3	±0.81
24hr	1.9	±0.64	**2.2**	±0.91

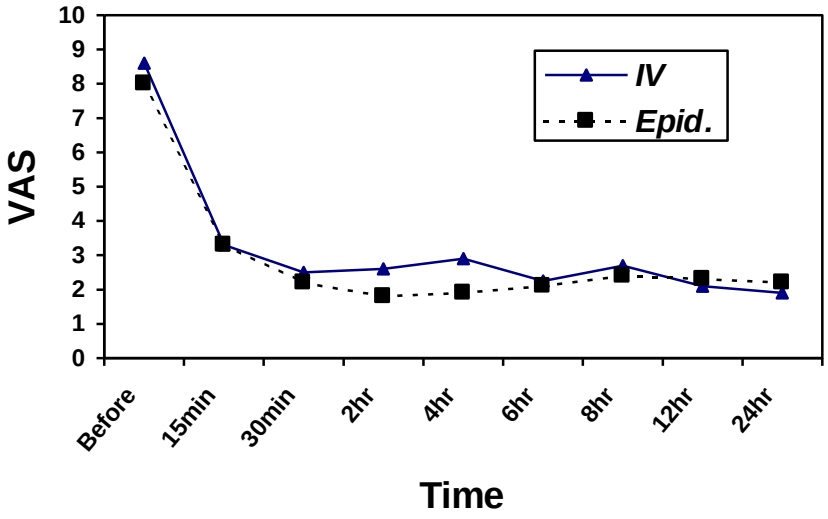

Figure 1 : Visual analogue scale (VAS). Values are represented as mean.

Table 4 : Respiratory rate changes. Values are represented as mean±SD. There are no inter-group differences. P value > 0.05.

time	Group I (IPCAA)		Group II(EPCA)	
	Mean	**SD**	**Mean**	**SD**
Before	**20.4**	**±2.10**	**20.8**	**±2.75**
15min	19.5	±2.51	20.4	±1.38
30min	19.0	±2.27	20.1	±2.37
4 hr	21.0	±2.82	20.7	±2.84
12hr	18.7	±1.94	20.0	±2.22
24hr	19.2	±1.89	**20.1**	±1.71

Table 5 : Changes in FVC and FEV1, values are represented as mean ±SD.*P value <0.05 compared with baseline.

	Pre- operative	**During** pain	**After 8 hr**	**After 24hr**
FVC				
Group I	3.68±0.67	0.64±0.23*	2.33±0.43*	2.81±0.44*
Group II	3.74±0.65	0.76±0.24*	2.04±0.53*	2.57±0.62*
FEV1				
Group I	2.60±0.71	0.46±0.35*	1.63±0.51*	1.94±0.53*
Group II	3.05±0.54	0.54±0.28*	1.61±0.45*	2.15±0.58*

Intravenous Group

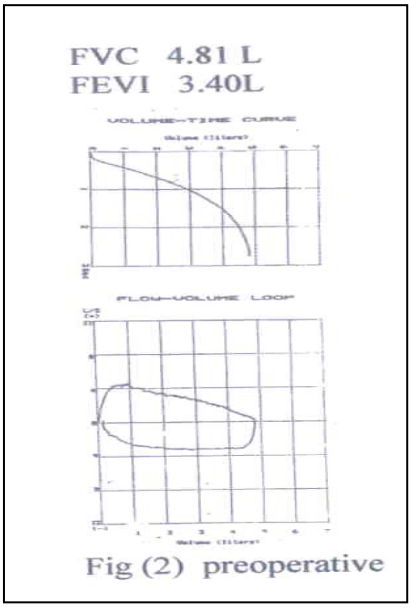

Fig (2) preoperative

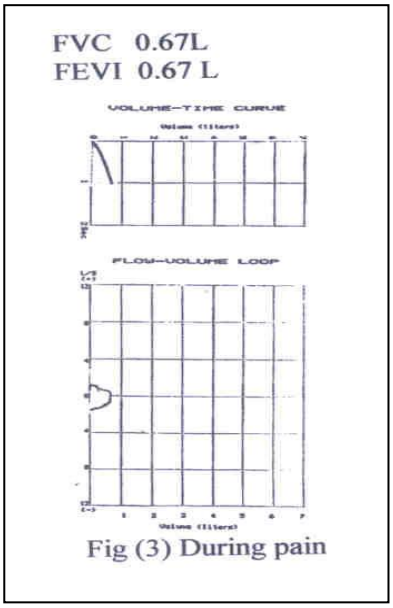

Fig (3) During pain

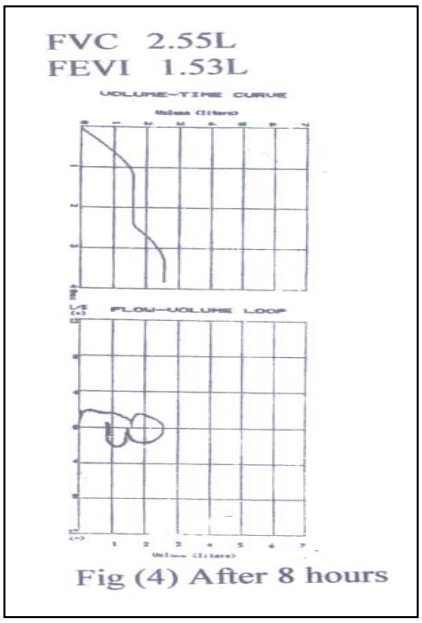

Fig (4) After 8 hours

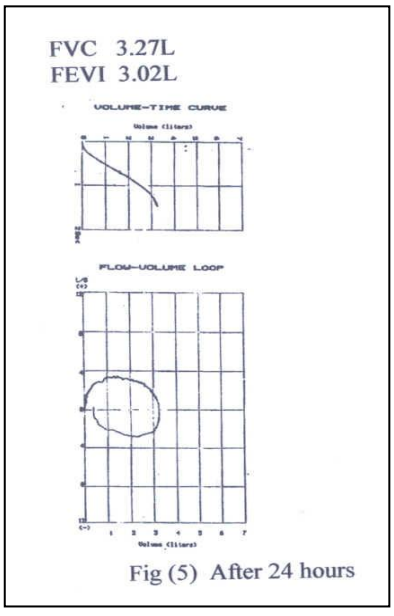

Fig (5) After 24 hours

Epidural group

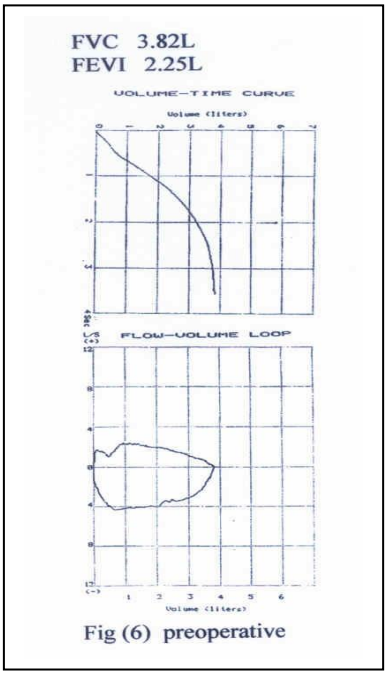

Fig (6) preoperative

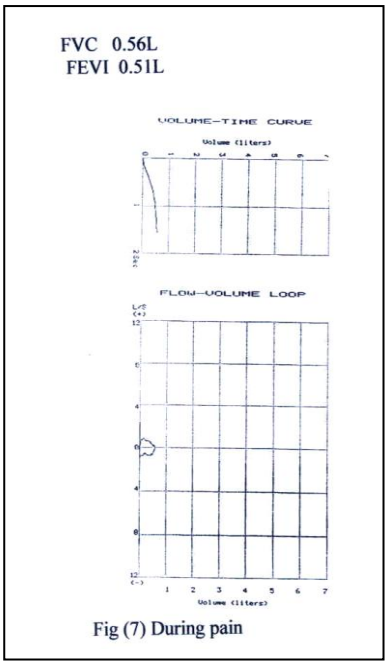

Fig (7) During pain

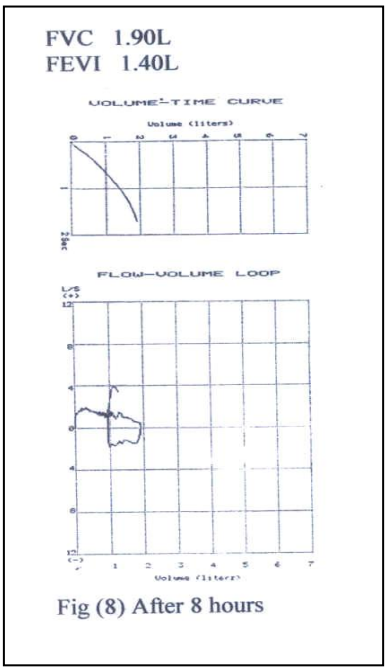

Fig (8) After 8 hours

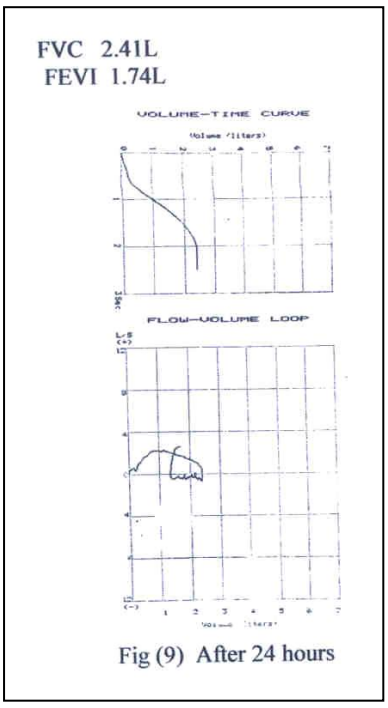

Fig (9) After 24 hours

Table 6 : Arterial blood gas analysis. Values are represented as mean ±SD. There are no inter-group differences.P value > 0.05.

	Before	**30min**	**4hr**	**24hr**
PH				
Group I	7.41±0.02	7.40±0.01	7.40±0.02	7.39±0.03
Group II	7.39±0.02	7.40±0.01	7.39±0.02	7.41±0.01
$PaCO_2$(mmHg)				
Group I	38±3.27	39±2.23	38±3.17	38±2.08
Group II	39±3.22	39±2.20	40±2.30	39±3.14
PaO_2(mmHg)				
Group I	88±10.47	89±8.69	89±7.09	90±8.31
Group II	92±8.38	90±8.72	90±9.21	89±7.81

Table 7 : Changes of beta-endorphin. Value are represented as mean±SD.P value > 0.05 compared to (pre-injection)

Time	**Group I (IPCAA)**		**Group II(EPCA)**	
	Mean	**SD**	**Mean**	**SD**
Before injection	22.8	±3.001	21.6	±4.333
After one hour	24.9	±3.636	23.2	±4.785

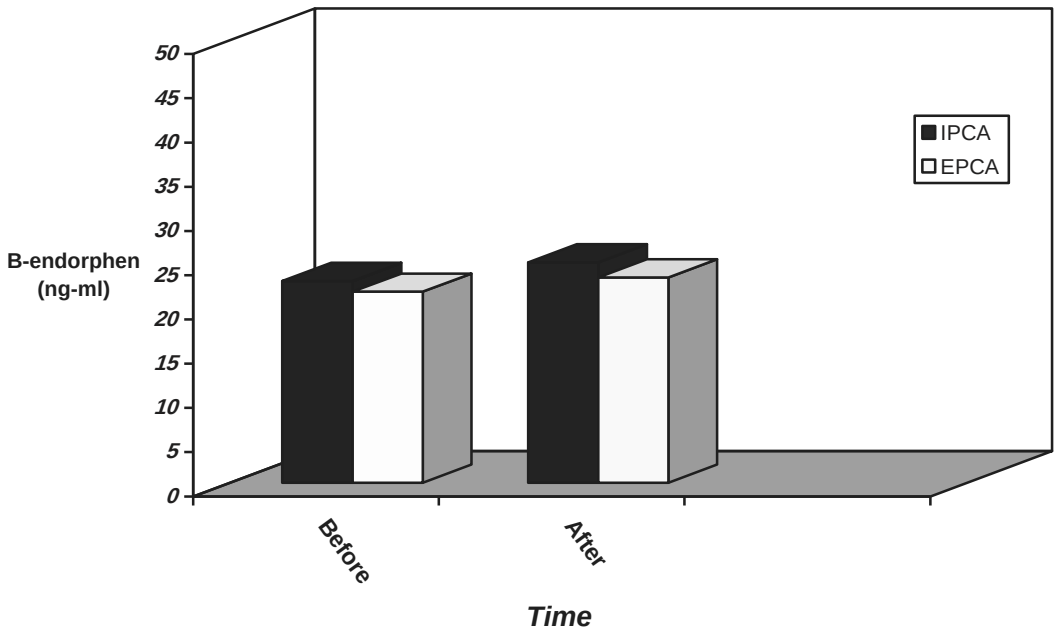

Figure10 : **Changes in plasma level of beta-endorphin. Values are represented as mean**

Discussion

Postoperative pain is a great problem that may cause indirectly, adverse effects on various organ syst - ems. The efficacy of clonidine admini - stration continue to be shown in acute postoperative pain management. It has been proved that epidural clonidine is an adequate alternative to opiates in prolonging the duration of analgesia provided by local anaesthetics (cook *et al.*, 1995).

Several attempts have been made to compare epidural and systemic administration of clonidine (De Kock *et al.*,1993).

This study investigated the analgesic and respiratory effects of clonidine when administered either intravenously or epidurally through patient controlled analgesia device. Clonidine was used as a sole analgesic after surgical procedures involving the abdomen or the lower extremities to assess whether these two administration routes were clinically equivalent and to document differences in doses required to achieve the same level of analgesia. In the present study intravenous or epidural doses ranging from 250-350µg of clonidine were given as an initial dose or 350 -500 µg as a total dose for pain relief which were relatively low doses if compared with other studies, as shown by Eisenach *et al*., 1989) who used clonidine doses ranging from 100-900µg (100µg increments) in patients following total knee, arthroplasty or abdominal surgery. Also de kock *et al*., (1993) used total dose of clonidine from 800-1000µg in his study. It has been proved that a fixed continuous infusion usually overestimates patient require - ments when compared to patient-controlled analgesia administration (Bouddreault *et al*.,1991). Bonnet *et al.*,(1989) observed that epidural clonidine 2µg/kg produced brief but significant pain relief after peripheral orthopedic surgery.

In this study, both intravenous and epidural clonidine administration, using patient-controlled analgesia device, provided complete postoperative analgesia. There was no significant difference in pain scores between the two groups. Reduction of clonidine requirements by the use of epidural route provides, indirect evidence that analgesia appears to be better after epidural than intravenous administration of clonidine, and clearly indicates that spinal cord is the main site for the analgesic addition of clonidine . this finding is consistent with the \work of (Eisenach *et al*., 1993) and (Bernard et al.,1995) who used clonidine epidurally and intravenously as a sole analgesic agent for postoperative pain relief. In contrast, the findings of Carroll *et al*., (1993) who reported that 150µg bolus dose of intravenous clonidine gives better results than the same dose admi - nistered epidurally

Restriction in respiratory funct - ions following surgical trauma was reported by different studies (Nishino *et al*., 1988) and it is common belief that good pain relief reduces the incidence of postoperative pulmonary complications.

In this study, respiratory rate and blood gases were unchanged through the study in both groups. No episodes of arterial oxygen saturation equal to or less than 95% were noted. These data were consistent with the results of (Berand *et al*., 1994) .

On the other side experimental studies showed that systemic clonidine had produced hypoxaemia in sheep (Eisenach and Dewan 1989) and epid - ural clonidine produced mild increase in arterial pco2 (Eisenach *et al*., 1993).

Restriction in respiratory function follo -wing surgical trauma was another similar study showing that intravenous but not intrathecal administration of alpha-2 adrenergic agonist results in substantial respiratory depression (Sabbe *et al.*,1994) .

In the present study, the onset of pain was accompanied by a severe restriction of pulmonary function test. The FVC and FEV1, were considerably and significantly reduced compared to preoperative levels in both groups. Pain relief with clonidine administration, resulted in a significant improvement in this reduction. However the values did not reach the preoperative level after 24 hr post injection.

It is well known that surgical trauma increases release of beta-endorphin level in plasma (Kehlet, 1987) levy,1986 reported that plasma level of beta-endorphin increases three folds after surgical incision and remains elevated well in the postoperative period.

In this study, plasma levels of beta-endorphin were increased in both groups after clonidine injection but levels were within the estimated range. The normal range of this peptide in plasma between 16-48 pg/ml. Sxyfelbein *et a*l., 1985 found that endorphin concentration was inversely proportional to acute pain, i.e. the greater the plasma concentration of B-endorphin the lower the reported pain. Plasma concentration of B-endorphin may be considered as a good indicator of endogenous pain modulation.

Conclusion

Clonidine proves to be adequate alternative to opiates without their side effects, like respiratory depression, itching, nausea and vomiting. It may be given by epidural or intravenous route for postoperative analgesia. The dose of clonidine is lower by the epidural route, indicating that it has specific action on sympathetic neurons of the spinal cord.

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المقارنة بين حقن الكلونيدين خارج الأم الجافية وحقنة فى الوريد لتسكين آلام ما بعد العمليات الجراحية بواسطة جهاز يتحكم فيه المريض

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د/ طارق محمد السعيد – د/ أمل محمد عبد الفتاح** –د/ أمل عبد العليم مرسى ****
أقسام التخدير والباثولوجيا الإكلينيكية بطب بنات الأزهر

إن العقاقير التى تميل الى مستقبلا ت الأدرينالين (ألفا 2) مثل الكلونيدين تختلف عن معظم العقاقير المهدئة فى إنها تسكن الألم بدون تأثير على عملية التنفس .

والغرض من هذا البحث هو المقارنة بين تأثير حقن الكلونيدين خارج الام الجافيه وحقنه فى الوريد على عملية التنفس وعلى إفراز الغدد الصماء بغرض تسكين الألم بعد العمليات الجراحية .

- اختير 40 مريضا من الجنسين من الفئة الاولى والثانية (تبعا لتقسيم الجمعية الأمريكية لأطباء التخدير) لعمل جراحات فى النصف الأسفل للبطن والأطراف السفلى وقسموا الى مجموعتين عدد كل مجموعة 20 مريضاً لدراسة تسكين الألم بعد العملية .
- أخذت المجموعة الاولى الكلونيدين عن طريق الحقن فى الوريد من خلال مضخة التحكم فى الألم بواسطة المريض .
- وأخذت المجموعة الثانية الكلونيدين عن طريق الحقن خارج الام الجافية من خلال مضخة التحكم فى الألم بواسطة المريض .
- بعد تخدير جميع المرضى تخدير عام ، أخذت منهم عينات دم شريانية ووريدية فى مواعيد متتالية وثابتة لقياس نسبة الغازات بالدم ونسبة الاندورفين فى البلازما .
- بعد انتهاء الجراحة إذا كان مقياس الألم النظرى اكثر من 4 أعطى للمريض جرعة أولى من الكلونيدين 4 ميكروجرام/كيلو عن طريق الوريد او خارج الأم الجافية على مدى نصف ساعة ثم يسمح لهم إعطاء العقار بأنفسهم عن طريق المضخة بمعدل 5ر ميكروجرام/كيلو فى الدقيقة مع فترة زمنية مغلقة بعد كل حقن مدتها 15 دقيقة للمجموعتين .

دلت النتائج ان الجرعة الكلية للكلونيدين كانت اقل فى مجموعة الحقن خارج الأم الجافية وان درجة الألم كانت أقل بعد إعطاء الكلونيدين فى المجموعتين عن قبل إعطاؤه ولكن ليس هناك فرق بين المجموعتين بعد إعطاؤه . وأيضا لم يكن هناك تغير فى معدل التنفس او فى نسبة الغازات بالدم فى المجموعتين ووجد أن (السعة الحيوية

بقـوة) وحجـم الزفيـر بقـوة فـى الثانيـة كانـت النسـبة قبـل إعطـاء الكلونيـدين فـى المجموعتين أقل من بعد إعطاؤه اما نسبة الاندورفين فى البلازما فزادت بعد ساعة من إعطاء الكلونيدين وليس هناك فرق بين المجموعتين .

نستنتج من هذا البحث ان الكلونيدين بديل مناسب لأشباه الأفيون لعلاج الام مابعد العمليات الجراحية مع عدم وجود آثار جانبية وان جرعة الكلونيدين تكون اقل إذا حقن خارج الأم الجافية عن حقنه فى الوريد .