The role of epidural neostigmine in postoperative analgesia.

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الملخص

اجريت هذه الدراسة لمقارنة كفاءة التسكين بعد العملية لحقن ثلاث جرعات مختلفة من عقار النيوستجمين خارج الام الجافية بالأضافة الى عقار الليدوكائين في عمليات التثبيت الخارجي لكسور عظم القصبة في مستشفى الديوانية التعليمي.خضع لهذه الدراسة 60 مريضا مقسمين الى اربعة مجموعات كل مجموعة تشتمل على 15 مريضا تتراوح اعمارهم بين 20-35 سنة و مصنفين من الدرجة الاولى بحسب تصنيف الرابطة الامريكية لاطباء التخدير.قسطرة خارج الام الجافية تتم قبل اعطاء التخدير العام و عند انتهاء العملية ستتلقى كل مجموعة احدى هذه الجرعات خارج الام الجافية :

1- المجموعة الاولى:يتلقون 4 مل من محلول ملح (نورمال سلاين) مع 4 مل من 0,75% ليدوكائين (مجموعة السيطرة).

2- المجموعة الثانية :يتلقون 4 مايكرو جرام/كغم نيوستجمين مخفف مع محلول ملح (نورمال سلاين)الى حجم 4 مل مع 4 مل 0,75%ليدوكائين.

3-المجموعة الثالثة :يتلقون 7 مايكروجرام/كغم نيوستجمين مخفف مع محلول ملح (نورمال سلاين)الى حجم 4 مل مع 4 مل 0,75% ليدوكائين .

4-المجموعة الرابعة :يتلقون 10 مايكرو جرام /كغم نيوستجمين مخفف مع محلول ملح (نورمال سلاين)الى حجم 4 مل مع 4 مل 0,75%ليدوكائين.لعلاج الالم بعد العملية تعطى تحاميل الديكلوفيناك 50 ملغ الى المريض حسب طلبه ثم اخذ الملاحظات الاتية خلال 24 ساعة: بعد الافاقة تم اخذ الملاحظات التالية:تغييرات ضغط الدم الشرياني و نبض القلب في الساعات (3و6و9و12و24) بعد العملية ،حساب مدة تسكين الالم من بعد انتهاء العملية وبداية الحقن وحتى طلب المريض اول جرعة مسكنة من تحاميل الديكلوفيناك ،تحديد عدد مرات طلب المسكن خلال 24 ساعة بعد انتهاء العملية وتحديد درجة التهدئة و تحديد عدد مرات الشعور بالغثيان او حدوث تقيء.اوضحت النتائج ان استخدام عقار النتوستجمين عن طريق الحقن خارج الام الجافية لم يؤدي الى اختلال ذي قيمة في نتائج قياسات الجهاز الوعائي القلبي وأن حقن 10 مايكرو غرام/كغم من عقار النتوستجمين خارج الام الجافية يزيد من معدل تسكين الالم بالمقارنة مع المجاميع الاخرى و كذلك يزيد من التهدئة في اول ثلاث ساعات بعد العملية مقارنة بالمجاميع الاخرى ولم يؤدي حقن عقار النيوستجمين خارج الام الجافية الى زيادة في معدل القيء او حدوث غثيان.و من هذه الدراسة نستنتج ان استخدام هذا العقار خارج الام الجافية بجرعة 10 مايكروغرام/كغم مع عقار الليدوكائين ادى الى زيادة معدل تسكين الالم دون تغييرلت مهمة او مضاعفات بعد العملية الجراحية.

Abstract

A prospective randomized study was performed for 60 adult male patients presented for external fixation of tibial fractures under general anaesthesia in Al-Diwaniya Teaching Hospital.All subjects according to American Society of Anaesthesiologist (ASA) classification were grade 1,between 20 – 35 of age. Before induction of general anaesthesia,an epidural catheter was inserted.At the end of surgery and recovery ,subjects were allocated into four groups (15 patients in each group):

Group 1 (n=15) received 4 ml of epidural saline with 4 ml of 0.75% lidocaine (control group).

Group 2 (n=15) received 4 ug|kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml of 0.75% lidocaine.

Group 3 (n=15) received 7 ug|kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml of 0.75% lidocaine.

Group 4 (n=15) received 10 ug|kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml of 0.75% lidocaine. All patients were assessed for 24 hours postoperatively for hemodynamic recording (heart rate and mean arterial blood pressure monitoring) at fixed intervals (3,6,9,12,24 hr) .For postoperative pain relief , diclofenac suppository was administered in increments of 50 mg on patient demand.The time from the end of surgery to first request, and the number of times diclofenac was requested in the first 24 hours after surgery , were recorded.Degree of sedation and number of postoperative nausea and vomiting were assessed.The aim of this study is to show the impact of addition of epidural neostigmine in three different doses with lidocaine or the use of epidural lidocaine alone on the postoperative analgesia following external fixation of tibial fractures.The result showed that the mean arterial blood pressure (MAP) and heart rate(HR) during the postoperative period showed significant decrease in the four groups compared to the baseline reading. However , the reduction was within 20% of the baseline and thus clinically acceptable and harmless.The postoperative analgesic duration(expressed as the time of first rescue analgesic supplementation of diclofenac suppository given) , was significantly longer in group 4 in comparison with other groups. The number of times diclofenac was requested during the first 24 hours after surgery were significantly lower in group 4 in comparison with other groups. Also there was no significant difference between the four groups as regarding postoperative nausea and vomiting. As regarding sedation , Group 4 has a significantly higher sedation score than the other groups in the first three hours postoperatively.Thus , it is concluded that postoperative epidural neostigmine in dose of 10 ug/kg, can provide a good postoperative analgesia , without side effect , when added to lidocaine and produces a longer duration of analgesia than lidocaine alone.

Introduction

Postoperative pain is the main postoperative complication which may affect the overall outcome , as it may cause delayed recovery from anaesthesia , delayed resumption of normal pulmonary function. An increase in the catabolic demands resulting in poor wound healing , weakness and muscle breakdown.It also increases the risk of thromboembolic events due to restriction of mobility.Sympathetic autonomic activation result in tachycardia and elevated blood pressure.Also poorly relieved pain has a negative psychological effect

causing sleeplessness and depression (*1). Epidural lidocaine has been widely used but may associated with many side effects like motor weakness , urinary retention , cardiovascular and central nervous system toxicity (*2). The efforts are applied to improves the postoperative epidural analgesia and minimizing its side effects. There have been also multiple comparisons of neuroaxial blockade to general anaesthesia , and a recent meta-analysis of these comparisons shows a significant reduction in mortality and morbidity with regional techniques (*3). Anumber of studies indicate that the dura does not represent a barrier to the movement of substances between the epidural and subarachnoid spaces (*4) . Local anaesthetics injected epidurally diffuses through the dura mater into the cerebrospinal fluid dependind on the physicochemical properties of these agents.A highly lipid soluble drug has been found to reach a greater depth in the spinal cord (*5).The cholinergic system is thought to modulate pain perception and transmission by a spinal mechanism by an interaction with muscarinic receptors.(*6).Intrathecal injection of cholinesterase inhibitors provides anti nociception by increasing acetylcholine in the cerebrospinal fluid(csf). Intrathecal neostigmine produces a dose-dependent analgesia without respiratory depression or hypotension and potentiates common spinal analgesics , such as local anaesthetics and opiates (*7). Unfortunately , after intrathecal injection , severe gastrointestinal side effects (nausia , vomiting , diarrhoea) occur and thus limits its routine clinical use. In contrast , epidural injection does not appear to be associated with these side effect. The analgesia mediated by epidural neostigmine is caused by the spread into the CSF at approximately 1/10th of the initial epidural dose(* 8).

Aim of the study

As the epidurally injected neostigmine decreases the the required dose of epidural local anaesthetics (hence , decreasing its side effects like motor weakness , urinary retention , cardiovascular and central nervous system toxicity) and potentiates common spinal analgesics(*9) , our aim is to find the precise effective dose of of neostigmine when combined with epidural lignocaine for postoperative analgesia.This study compare the postoperative analgesic effeciency of three different doses of neostigmine when combined with lidocaine after external fixation of tibial fractures.Comparison is based on the analgesia obtained , the sedation level , the haemodynamic stability and any possible side effects.

Patients and Methods

60 adult male(*10) patients (20 – 35 years old , ASA 1 classification) are the material of this study.All patients were scheduled for external fixation of tibial fractures at Al-Diwanyia Teaching Hospital.

Patients were randomly divided into four groups each composed of 15 patients.Exclusion criteria in this study included any contraindications to epidural anaesthesia , morbid obesity and patients with abnormal hepatic or renal function (*11).Preoperative: History, examination and reviewing of the investigation for every patient were checked before surgery to fulfill the inclusion criteria for this study.The procedure, its risk and benefit were explained to the patient, and questions were answered.No premedication had been given.Intraoperative: After establishing an I.V. line , all patients received 1000 ml of lactated ringer solution , an epidural catheter was inserted in the operating room in all patients at L3-L4 intervertebral space.Test dose of 4ml lidocaine 2 % with adrenaline 1/100000 to exclude intravascular or subarachnoid position of the catheter. Monitoring include lead 2 ECG , non invasive blood pressure monitor & pulse oximetry.Basline haemodynamic readings were taken including heart rate , blood pressure & oxygen saturation.Induction of anaesthesia was performed using thiopentone (3-5 mg / kg) and tracheal intubation was facilitated by atracurium (0.5 mg / kg).Anaesthesia was maintained with halothane / O2. Lungs were mechanically ventilated with tidal volume of 7 – 10 ml / kg and respiratory rate 12 / min. During anaesthesia arterial blood pressure , heart rate &haemoglobine oxygen saturation were regularly monitored.Patients had been randomly divided into four groups , each group contain 15 patients . At the time of wound closure patients received one of four epidural solution

1- Patient group 1 (n = 15) will receive 4 ml of epidural saline with 4 ml lidocaine 0.75% (control group).

2- Patient group 2 (n = 15) will receive 4 microgram/ kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml lidocaine 0.75% .

3- Patient group 3 (n = 15) will receive 7 microgram/ kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml lidocaine 0.75%.

4- Patient group 4 (n = 15) will receive 10 microgram /kg epidural neostigmine diluted with normal saline to a total 4 ml volume with 4 ml lidocaine 0.75 %.The epidural catheter was removed at the operating room.Postoperative: After reversal of muscle relaxant and tracheal extubation , patient had been transferred to recovery room and monitored with ECG , blood pressure and oxygen saturation.

Data Collected

1- Patient age , weight , height and surgery time.

2- All patients were assessed for 24 hours postoperatively.

3- Haemodynamic recording (heart rate and mean arterial blood pressure monitoring) at fixed intervals (3 , 6 , 9 , 12 , 24 hours) .

4- Degree of sedation recorded at fixed intervals (3 , 6 , 9 hours) postoperatively (Ramsey sedation score) (*12).
0 = Alert or drowsy
1 = sleepy but arousable by verbal command.
2 = sleepy but arousable by tactile command.
3 = sleepy but not arousable by tactile command.
5-Number of postoperative nausea and vomiting were recorded. Postoperative nausea and vomiting were treated with 10 mg I.V. metoclopramide on patient demand.
For postoperative pain relief , diclofenac suppository given in increments of 50 mg on patient demand , and no other drugs were used for analgesia. The time from the end of surgery to first request , and the number of times diclofenac was requested in the first 24 hours after surgery , were recorded.

Results

1- No significant difference in the demographic data of the patients as regards age , weight , height , and surgery time between the four studies (table 1).
2- Haemodynamic data (mean blood pressure and heart rate)during postoperative period shows significant decrease in the four groups compared to the baseline reading , though there was no significant difference in between the four groups. However, the reduction was within 20% of baseline reading and thus clinically acceptable and harmless.(table 2) (table 3).
3- The postoperative analgesic duration (as expressed as the time of first rescue analgesic supplementation of diclofenac suppository given),was significantly longer in group 4 in comparison with group 1 , group 2 and group 3.(table 4).
4- The number of time diclofenac was requested during the first 24 hours after surgery were significantly lower in group 4 in comparison with group 1 , group 2 and group 3 (table 4). All patients received at least one rescue administration during the first 24 hours after surgery.
5- There was no significant difference between the four groups as regarding postoperative nausea and vomiting (table 5).
6- Group 4 has a significant higher sedation score than the other groups in the first 3 hours postoperatively.Sedation was mild in nearly all cases and did not adversely affect satisfaction. (table 6).

Table- 1 : demographic data for the four groups regarding age , weight , height and surgery time

	GROUP	1	GROUP	2	GROUP	3	GROUP	4
Variable	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
Age (yrs)	28.3	5.7	29.7	5.6	27.5	4.1	30.5	4.9
Weight (kg)	78.6	9.6	80.8	8.9	83.3	8.3	85.8	9.5
Height (cm)	174	6.9	175.7	7.4	173.4	7.2	170.1	7.1
Surgery time	79.5	9.3	85.5	7.5	85.8	10.7	80.3	9.9

Table -2 : shows the change in the mean arterial blood pressure (MAP) in the four studied groups before epidural injection and at various times within the 24 hours following the epidural injection.

MAP (mmhg)	Group	Mean	Std . Deviation
Baseline	Group 1	94.3	6.9
	Group 2	89.1	8.1
	Group 3	93.3	7.6
	Group 4	91.3	7.9
3 hours	Group 1	80.1	9.2
	Group 2	81.3	8.4
	Group 3	79.5	6.6
	Group 4	75.2	8.1
6 hours	Group 1	79.0	11.3
	Group 2	81.6	7.9
	Group 3	82.5	7.4
	Group 4	81.6	8.4
9 hours	Group 1	82.5	9.6
	Group 2	81.3	7.1
	Group 3	82.3	6.6
	Group 4	79.0	7.4
12 hours	Group 1	85.8	6.8
	Group 2	83.3	7.1
	Group 3	83.5	6.6
	Group 4	84.7	7.6
24 hours	Group 1	89.8	7.1
	Group 2	87.6	6.6
	Group 3	87.4	7.4
	Group 4	88.7	7.7

Table- 3 : shows the changes in the heart rate (H.R.) in the four studied groups before epidural injection and at various times within the 24 hours following the epidural injection.

Heart rate (BPM)	Gropes	Mean	Std. Deviation
Baseline	Grop1	98.1	5.8
	Grop2	96.7	50.3
	Grop3	95.5	6.2
	Grop4	97.3	5.4
3 hours	Grop1	89.2	5.2
	Grop2	90.5	5.5
	Grop3	88.9	5.9
	Grop4	87.2	5.6
6 hours	Grop1	86.5	6.1
	Grop2	87.3	5.1
	Grop3	85.6	6.2
	Grop4	84.7	6.1
9 hours	Grop1	84.3	5.1
	Grop2	83.9	4.9
	Grop3	82.6	5.3
	Grop4	80.5	4.8
12 hours	Grop1	84.1	4.9
	Grop2	84.2	4.6
	Grop3	82.9	4.1
	Grop4	82.1	4.2
24 hours	Grop1	82.3	3.8
	Grop2	83.1	4.1
	Grop3	83.3	4.3
	Grop4	82.5	4.9

Table- 4:Analgesic duration expressed in minutes , in the four groups calculated from the first diclofenac supplementation postoperatively and the number of times diclofenac was requested during the first 24 hours after surgery.

Variables	Group 1	Group 2	Group 3	Group 4
Time to fisrt diclofenac (min)	80 (60-90)	85 (70-110)	90(70-115)	210(190-240)
Number of diclofenac (n)	3 (2-4)	2(2-2.5)	2(2-3)	1(1-2)

Table - 5: postoperative nausea & vomiting

Group 1 number & (%)	Group2 number & (%)	Group 3 number & (%)	Group 4 nmber & (%)
3 (20%)	4 (26.7%)	6 (40%)	6 (40%)

Table-6:Gr.4 has a significant higher sedation score than the other groups

		Group	Group2	Group 3	Group4
3 hours postoperative	Score0	14(93.3%)	14(93.3%)	13(86.7%)	8(53%)
	Score1	1(6.7%)	1(6.7%)	2(13.3%)	5(33.3%)
	Score2	0 (0%)	0 (0%)	0(0%)	2(13.3%)
	Score3	0 (0%)	0 (0%)	0(0%)	0(0%)
6 hours postoperative	Score0	15(100%)	13(86%)	14(93.3%)	13(86.7%)
	Score1	0 (0%)	2(13.3%)	1(6.7%)	2(13.3%)
	Score2	0 (0%)	0(0%)	0(0%)	0(0%)
	Score3	0 (0%)	0(0%)	0(0%)	0(0%)
9 hours postoperative	Score0	15(100%)	15(100%)	15(100%)	15(100%)
	Score1	0 (0%)	0(0%)	0(0%)	0(0%)
	Score2	0 (0%)	0(0%)	0(0%)	0(0%)
	Score3	0 (0%)	0(0%)	0(0%)	0(0%)

Conclusions

Considering the result of this study , it showed that the addition of neostigmine in a dose 10 microgram/kg had an augmented effect on the analgesia achieved by the epidurally injected lidocaine and significantly extended the analgesic effect in the postoperative period and reducing the need for supplementation pain killers.

It was proved that , this was associated with mild sedation with no haemodynamic instability and without significant nausea or vomiting which was the most troublesome side effect during intrathecal administration of the drug (*13).Therefore , neostigmine could represent a new non opiod adjunct for postoperative analgesia.

In conclusion , 10 microgram/kg of epidural neostigmine in lidocaine provides a useful tool for treatment of postoperative pain after external fixation of tibial fractures and produces a longer duration of analgesia than lidocaine alone or with the use of 4 microgram / kg or 7 microgram / kg of epidural neostigmine without increasing the incidence of adverse effects.

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