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Prophylactic epidural administration of fentanyl for the suppression of tourniquet pain

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Abstract: Severe dull pain on the side of tourniquet application and marked rises in blood pressure and heart rate associated with that pain are often observed even under adequate regional analgesia. The purpose of this study was to evaluate the effect of epidural fentanyl on the suppression of tourniquet pain during orthopedic surgical procedures. Forty-five patients undergoing orthopedic surgery of the lower extremities with a tourniquet were maintained by continuous epidural anesthesia with 2% lidocaine through an epidural indwelling polyethylene catheter (L3–4). The patients were randomly allocated to the following three groups: epidural fentanyl (100 μg) (epidural group, $n = 15$); intravenous fentanyl (100 μg) (intravenous group, $n = 15$); control (no fentanyl) (control group, $n = 15$). The epidural or intravenous fentanyl was administered at the time of the second lidocaine injection. The severity of tourniquet pain based on the patient's level of complaint and the total dose of supplemental analgesics requested in the epidural group were significantly lower than those in the control group. Blood pressure during tourniquet application in the epidural group was more stable than in the other two groups. No severe side-effects were observed in any patient. Prophylactic epidural administration of fentanyl might be useful in the suppression of tourniquet pain.

Key words: Tourniquet pain, Epidural fentanyl, Prophylactic administration

Introduction

Tourniquet pain is considered to be transmitted by small nonmyelinated fibers (C fibers) along the sympathetic trunks which enter the cord at a level cephalad to the sensory block [1,2]. Severe dull pain on the side of tourniquet application and marked rises in blood pressure and heart rate associated with that pain are often observed even under adequate regional analgesia of the surgical field. Although high sensory blockade with a large amount of local anesthetic might resolve the problem, it would be accompanied by undesirable complications such as hypotension or local anesthetic intoxication, especially in geriatric patients. Epidural fentanyl has been reported to be useful in the alleviation of postoperative pain [3,4]. Furthermore, the concept of preemptive analgesia has also recently attracted a great deal of attention [5]. The purpose of this study was to evaluate the effect of epidural fentanyl on the suppression of tourniquet pain during orthopedic surgical procedures.

Materials and methods

After obtaining approval from the Institutional Ethics Committee on Human Research at our facility, we studied 45 adult patients (ASA physical status 1) scheduled for elective orthopedic surgery of a lower extremity with application of a tourniquet around the thigh. Informed consent was obtained from all of the subjects.

The patients received no premedication. After placement of an intravenous catheter in the forearm, lactated Ringer's solution was administered at the rate of $10\,ml \cdot kg^{-1} \cdot h^{-1}$. A blood-pressure cuff and electrodes for electrocardiography were also applied. A polyethylene catheter, with a diameter of 0.8 mm, was introduced into the epidural space at the L3–4 interspace with the patient in the lateral decubitus position. Absence of back flow of blood or cerebrospinal fluid was confirmed by gentle aspiration before a local anesthetic was injected into the epidural catheter. First, a test dose of local anesthetic (2 ml of 2% lidocaine) was injected into the catheter, and it was confirmed that the tip of the catheter was not located in the subarachnoid space. The initial dose of $0.25\,ml \cdot kg^{-1}$ of 2% lidocaine was then

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injected into the epidural space. Subsequently, half of the initial dose of lidocaine was injected every 30 min after the initial injection to maintain the regional block. The subjects were randomly allocated to an epidural fentanyl group (Epi., $n = 15$), an intravenous fentanyl group (IV, $n = 15$) or a control group (Cont., $n = 15$). In the Epi. group, 100 μg of fentanyl was administered epidurally concomitantly with the second epidural injection of lidocaine after confirming the effect of regional blockade with the initial lidocaine, which was given before the patient complained of tourniquet pain. In the IV group, 100 μg of fentanyl was administered intravenously at the time of the second epidural injection of lidocaine. In the Cont. group, only lidocaine was administered.

The leg on the surgical side was exsanguinated by winding an Esmarch rubber bandage tightly up the thigh. A pneumatic tourniquet (Model A.T.S. 1500, Englewood, CO, USA) secured loosely around the middle of the thigh was then inflated to a pressure of 450 mmHg. We noted the complaints of the patient every 10 min during the tourniquet procedure. Subsequently, the severity of pain during the tourniquet procedure was graded according to the patient's level of complaint as follows: grade A indicated no request, and grade B indicated a request for analgesic and or sedative. In subsequent reclassification, grade A included no pain (no complaints) and mild pain (no request for analgesic or sedative), and grade B included moderate pain (request for analgesic and/or sedative) and severe pain (request for analgesic/sedative and the need for nitrous oxide inhalation). When the patient complained of the tourniquet pain and requested analgesics and/or sedatives during the tourniquet procedure, 0.5 mg butorphanol i.v. (maximum dose 1 mg during the tourniquet procedure) and/or 1 mg midazolam i.v. (maximum dose 5 mg during the tourniquet procedure) were administered incrementally. In patients with severe tourniquet pain, 50% nitrous oxide was also administered by mask inhalation at the discretion of the anesthesiologist.

The extents of hypalgesia and analgesia in the dermatome were determined by the cold sign and pin-prick methods, respectively, 30 min after the initial injection of lidocaine and also at the end of surgery. Blood pressure (BP) and heart rate (HR) were measured automatically (BP-308E, Nippon Colin, Komaki City, Japan) every 5 min. Both BP and HR were measured before lidocaine injection (T_0), immediately before (T_1) and after (T_2) tourniquet inflation, and immediately before (T_3) and after (T_4) tourniquet deflation. BP stability during tourniquet application and at tourniquet deflation was expressed according to the following formulae: $(T_3BP - T_2BP)/T_2BP \times 100(\%)$ and $(T_4BP - T_3BP)/T_3BP \times 100(\%)$, respectively. Arterial blood gases were measured (ABL330, Radiometer, Copenhagen, Denmark) before the start of epidural anesthesia and after the completion of surgery to investigate the respiratory effects of fentanyl.

The period of postoperative analgesia was taken to be the time from arrival at the ward to the patient's first request for analgesics for pain relief. The incidence of side-effects, including respiratory depression, nausea, vomiting, pruritus, and urinary retention in patients without a balloon bladder catheter was recorded for 24 h after the end of the operation.

Values are expressed as mean ± SD. Data were analyzed using the one- or two-way analysis of variance with repeated measurement, followed by Fisher's test, Sheffe's F-test, or the Mann–Whitney test. A P value of less than 0.05 was considered to be significant.

Results

The surgical procedures conducted on the lower extremities of the patients in each group are summarized in Table 1. Table 2 shows the patient's characteristics, duration of tourniquet application, time from tourniquet inflation to fentanyl administration, rostral extent of epidural anesthesia, and amount of i.v. crystalloid fluid administered in each group. There were no significant differences among the three groups in any of the above parameters.

BP at T_3 in the Epi. group was lower ($P < 0.05$) than that in the Cont. group (Table 3). BP change during tourniquet application in the Epi. group was lower than in the other two groups, although the differences were not significant. The reduction in BP at tourniquet deflation in the Epi. group was less marked than those in the IV group (systolic BP; $P < 0.05$) or in the Cont. group (diastolic BP; $P < 0.05$), as indicated in Table 4.

The number of patients who did not require the analgesics and/or sedatives (grade A) in the Epi. group was significantly higher than in the Cont. group ($P < 0.05$). Furthermore, the number of patients who did not complain of tourniquet pain (painless grade) in the Epi. group was significantly higher than in the Cont. group and the IV group ($P < 0.05$), as shown in Table 5. The total amounts of butorphanol given in the Epi., Cont., and IV groups were 0 ± 0, 0.33 ± 0.45, and 0.13 ± 0.35 mg, respectively. The total amount of butorphanol given in the Epi. group was significantly lower than in the Cont. group ($P < 0.05$). The total amounts of midazolam given in the Epi., Cont., and IV groups were 0.73 ± 1.28, 1.80 ± 1.83, and 1.13 ± 1.13 mg, respectively. There were no significant differences among the groups in the dosage of midazolam. Postoperative analgesia was not significantly different (Epi., Cont., and IV

Table 1. Surgical procedures on the lower extremities in each group

Group	Surgical procedures	Number of patients
Epi. (n = 15)	Knee joint surgery	8
	Osteosynthesis of tibia and high tibial osteotomy	5
	Ankle joint surgery	2
IV (n = 15)	Knee joint surgery	7
	Osteosynthesis of tibia and high tibial osteotomy	6
	Ankle joint surgery	1
	Extraction of Küntcher nail and curettage of the tibial bone	1
Cont. (n = 15)	Knee Joint surgery	5
	Osteosynthesis of tibia and high tibial osteotomy	5
	Ankle joint and forefoot surgery	4
	Curettage of the peroneal bone and bone grafting	1
		45

Epi., epidural fentanyl group; IV, intravenous fentanyl group; Cont., control group (no fentanyl).

Table 2. Patient characteristics, duration of tourniquet application, time from tourniquet inflation to fentanyl administration, rostral extent of epidural anesthesia, and amount of i.v. crystalloid fluid administered in each group

	Epi. group	IV group	Cont. group
Age (years)	48.6 ± 12.3	50.1 ± 20.9	49.2 ± 18.1
Height (cm)	157.3 ± 8.3	155.8 ± 8.2	161.2 ± 11.1
Weight (kg)	59.0 ± 11.8	58.5 ± 10.4	60.3 ± 12.0
Duration of tourniquet application (min)	105.9 ± 34.8	91.3 ± 29.4	103.4 ± 30.1
Time from tourniquet inflation to fentanyl administration (min)	17.2 ± 6.3	14.2 ± 8.1	
Initial dose of 2% lidocaine (ml)	13.3 ± 1.8	13.0 ± 2.1	13.3 ± 1.8
Total dose of 2% lidocaine (ml)	33.2 ± 8.7	32.7 ± 10.0	34.3 ± 7.1
Rostral extent of analgesia			
Immediately before surgery	Th 9.1 ± 2.8	Th 10.6 ± 2.4	Th 10.7 ± 2.9
Immediately after surgery	Th 9.7 ± 2.9	Th 9.7 ± 2.6	Th 10.3 ± 2.0
Rostral extent of hypalgesia			
Immediately before surgery	Th 7.3 ± 2.9	Th 8.3 ± 2.9	Th 8.7 ± 3.0
Immediately after surgery	Th 6.9 ± 2.5	Th 7.5 ± 2.8	Th 8.2 ± 2.4
Total amount of i.v. crystalloid fluid (ml)	1177 ± 249	1275 ± 396	1117 ± 377

Data are expressed as mean ± SD.

groups were 628.3 ± 531.2, 777.7 ± 653.2, and 695.7 ± 592.1 min, respectively.). Nausea during the intraoperative and postoperative 24-h period was noted in 3 (20%) of the 15 patients in the Epi. group, 0 (0%) of 15 in the Cont. group, and 6 (40%) of 15 in the IV group ($P < 0.05$ compared with the Cont. group). Urinary retention was noted in 1 (20%) of the 5 patients without a balloon bladder catheter in the Epi. group, 2 (25%) of 8 in the Cont. group, and 1 (11%) of 9 in the IV group. There were no significant differences among the groups. Other side-effects, such as pruritus and life-threatening respiratory depression, were not observed in any group. There were no significant differences among the groups in arterial pH or blood gas tensions determined before or after surgery.

Discussion

The tourniquet procedure is often applied to patients repeatedly during the course of orthopedic surgery of the lower extremities. Our clinical experience has revealed that a patient who has already complained of tourniquet pain during the first tourniquet application is

Table 3. Sequential changes of heart rate and blood pressure in each group

	Group	T_0	T_1	T_2	T_3	T_4
HR (beats min^{-1})	Epi.	86.9 ± 17.3	82.4 ± 14.9	81.3 ± 13.9	78.5 ± 14.3	81.5 ± 14.0
	IV.	75.5 ± 13.8	75.3 ± 19.3	74.0 ± 20.6	71.0 ± 12.0	77.0 ± 11.8
	Cont.	75.0 ± 13.4	81.2 ± 13.4	81.1 ± 14.3	80.5 ± 13.0	83.3 ± 13.3
SBP (mmHg)	Epi.	137.5 ± 21.2	116.0 ± 11.7	116.3 ± 13.5	113.1 ± 14.1*	107.9 ± 15.2
	IV	139.4 ± 21.8	117.5 ± 17.9	123.5 ± 23.6	128.8 ± 17.6	114.7 ± 15.2
	Cont.	134.1 ± 15.7	119.3 ± 21.3	124.7 ± 20.4	130.8 ± 26.0	116.7 ± 15.0
DBP (mmHg)	Epi.	78.5 ± 10.2	65.8 ± 7.5	66.3 ± 7.2	67.3 ± 7.8**	63.1 ± 9.2
	IV	82.0 ± 12.1	65.4 ± 11.3	70.2 ± 14.4	73.2 ± 10.5	64.5 ± 10.4
	Cont.	76.2 ± 11.2	69.4 ± 11.0	71.8 ± 10.8	77.1 ± 13.7	66.3 ± 9.0
MBP (mmHg)	Epi.	98.1 ± 13.1	82.5 ± 8.1	83.1 ± 8.7	82.6 ± 9.5**	78.0 ± 10.8
	IV	103.7 ± 13.0	83.5 ± 15.2	90.4 ± 17.2	93.2 ± 10.5	82.7 ± 10.8
	Cont.	95.4 ± 11.0	86.1 ± 13.9	89.5 ± 13.3	95.0 ± 17.2	83.2 ± 9.7

Data are expressed as mean ± SD.
T_0, before initial epidural injection of lidocaine; T_1, immediately before tourniquet inflation; T_2, immediately after tourniquet inflation; T_3, immediately before tourniquet deflation; T_4, immediately after tourniquet deflation. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.
* $P < 0.05$ Epi. vs. IV and Cont.; ** $P < 0.05$ Epi. vs. Cont.

Table 4. Change in blood pressure during tourniquet application and at tourniquet deflation in each group

	Group	During tourniquet application $(T_3 - T_2)/T_2$ (%)	At tourniquet deflation $(T_4 - T_3)/T_3$ (%)
SBP	Epi.	−2.6 ± 5.0	−4.7 ± 6.0*
	IV	5.8 ± 13.8	−10.7 ± 5.7
	Cont.	6.2 ± 20.3	−9.4 ± 10.5
DBP	Epi.	1.8 ± 8.9	−6.4 ± 6.5**
	IV	6.0 ± 13.2	−13.0 ± 10.0
	Cont.	8.5 ± 19.9	−11.8 ± 8.4
MBP	Epi.	−0.5 ± 6.0	−5.7 ± 5.7
	IV	5.8 ± 13.1	−11.2 ± 9.8
	Cont.	7.3 ± 19.6	−11.2 ± 6.5

Data are expressed as mean ± SD.
SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.
* $P < 0.05$ Epi. vs. IV; ** $P < 0.05$ Epi. vs. Cont.

Table 5. Severity classification for tourniquet pain in each group ($n = 15$)

	Grade A		Grade B	
Group	No pain	Mild pain	Moderate pain	Severe pain
Epi. (%)	12 (80)*,a	3 (20)*	0 (0)	0 (0)
Cont. (%)	5 (33.3)	5 (33.3)	4 (26.7)	1 (6.7)
IV (%)	5 (33.3)	8 (53.3)	1 (6.7)	1 (6.7)

Grade A, no request for analgesic/sedative; Grade B, request for analgesic/sedative.
No pain, no complaint; mild pain, no request for analgesic/sedative; moderate pain, request for analgesic/sedative; severe pain, request for analgesic/sedative and N_2O inhalation.
* $P < 0.05$ Epi. vs. Cont. in Grade A; [a] $P < 0.05$ Epi. vs. Cont. and IV in the no pain.

likely to complain of tourniquet pain soon after the start of the second tourniquet application. Tourniquet procedure management is very challenging for anesthesiologists. Recently, Katz et al. [6] found that a single dose of epidural fentanyl ($4\,\mu g \cdot kg^{-1}$) given prior to the start of surgery was more effective than that given postoperatively in reducing pain and analgesic requirement between 12 and 24h after thoracotomy. We also thought that preemptive analgesia might be a useful strategy for the management of tourniquet pain. Therefore, we administered the epidural or intravenous fentanyl in advance of the patient's complaint of tourniquet pain in the present study. We observed a significant reduction of the pain severity grade and the require-

ment for supplemental analgesics in the Epi. group compared with the Cont. group. In response to tourniquet pain, the sympathetic nervous system is thought to be activated, causing hypertension and/or tachycardia. However, BP in the Epi. group patients remained relatively stable during tourniquet application. This finding suggests that prophylactic epidural fentanyl may be useful in the suppression of tourniquet pain and of sympathetic responses to the noxious stimulation.

There was no significant difference between the Cont. group and the IV group in grade A patients (no request for analgesic and/or sedative), and the number of patients in the no pain grade (no complaint) was significantly higher in the Epi. group than in the IV group. These results suggest that prophylactic IV fentanyl was not so effective in the suppression of tourniquet pain. We considered that some different mechanism might exist for the suppression of tourniquet pain after epidural administration or intravenous injection of fentanyl. It might be that epidural fentanyl, in addition to its systemic action, acts directly on the opioid receptors in the dorsal horn of the spinal cord after penetration into the cerebrospinal fluid through the dura mater. The potency of 100 μg intravenous fentanyl administration might not be same as that of epidural administration even if the same dose was administered [7].

Epidural or intrathecal morphine has been used for the past decade to relieve postoperative pain. However, several side-effects, including nausea, vomiting, urinary retention, pruritus and life-threatening delayed respiratory depression, are still reported [8,9]. Such sustained side-effects may delay postoperative rehabilitation. Furthermore, as the analgesic effects of epidural morphine are not manifest until 30–40 min after administration [10], the action of epidural morphine may not be rapid enough to block the tourniquet pain. Fentanyl, a highly lipid-soluble opioid, shows shorter-term action and more rapid onset of analgesia compared with morphine. Life-threatening respiratory depression is reported to be rare in the postoperative period, since epidurally administered fentanyl tends to spread segmentally even when it is given continuously [11,12]. Because of the properties of fentanyl, including its more rapid onset and shorter-term action, it would seem to be the most appropriate epidurally administered opioid for the treatment of tourniquet pain.

In none of our groups were any severe side-effects, such as life-threatening respiratory depression in the perioperative period, observed. However, antiemetics might be required in the IV group because of the high incidence of nausea. In patients with urinary retention after epidural fentanyl, we recommend single bladder catheterization, because the effects of epidural fentanyl disappear within a few hours.

We could not clarify whether the preemptive administration of fentanyl resulted in more effective tourniquet pain management, because in this study we did not compare the analgesic effects before and after the development of tourniquet pain. The optimal amount, injection site, and timing of epidural fentanyl remain to be investigated.

In conclusion, patients given epidural fentanyl showed significantly lower-grade severity of tourniquet pain and required a significantly lower total amount of supplemental analgesic than control patients given lidocaine alone. Furthermore, during the tourniquet application the blood pressure of patients given epidural fentanyl was comparatively more stable. No severe side-effects of epidural fentanyl were noted. We recommend prophylactic epidural fentanyl combined with 2% lidocaine to reduce the development of tourniquet pain in patients undergoing orthopedic surgery of the lower extremities.

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