THE IMPACT OF LONG-LASTING PREEMPTIVE EPIDURAL ANALGESIA BEFORE TOTAL HIP REPLACEMENT ON THE HORMONAL STRESS RESPONSE. A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND STUDY.

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Abstract

Recent studies suggest that preemptive analgesia may be effective in reducing postoperative pain. One physiologic explanation may be interference with the endogenous opioid response. We investigated whether long-lasting preoperative preemptive analgesia may have an effect on the hormonal stress response after total hip replacement.

Methods

42 patients scheduled for elective hip replacement for coxarthrosis were randomized to receive, on the day before the operation, either 5 ml*h^{-1} ropivacaine 0.2% (study group, n = 21) or 5 ml*h^{-1} saline (control group, n = 21). Postoperative analgesia was achieved in both groups by patient-controlled epidural analgesia (PCEA) with ropivacaine 0.2%. The main outcome measure was the concentration of authentic ß-endorphin [1-31] in plasma up to 4 days after surgery. Additional parameters included concentrations of adrenocorticotrope hormone and cortisol.

Results

Both groups were comparable concerning preoperative parameters and pain scores. Epidural blocks were sufficient in all patients for operative analgesia. Preemptive analgesia was performed for 11-20 hours in both groups and led to significantly decreased pain scores before surgery. Preemptive analgesia with epidural ropivacaine did not lead to decreased concentrations of ß-endorphin [1-31] before the start of surgery or in the postoperative period. Furthermore, no differences could be detected in the time course of ß-endorphin and adrenocorticotrope hormone after surgery. However, cortisol concentrations differed significantly between groups before the operation, but showed a comparable rise after surgery.

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Conclusion

Differences in postoperative pain after preemptive analgesia do not seem to be due to an altered endogenous opioid response.

Introduction

The effect of preemptive analgesia upon postoperative outcome remains controversial[1]. Agents under investigation for a possible effect include opioids[2], ketamine[3], local anesthetics[4], and other analgesics[5,6]. Possible explanations for the preemptive effect on postsurgical pain include reduction of nociceptive input, increasing the threshold of nociception, and prevention of neuronal sensitization [7]. The suggested ways of interaction may be mediated by NMDA- or opioid-receptors, inhibition of cyclooxygenase, and interference with α2-antagonists[7]. In the case of opioids, peripheral as well as central receptors may play an important role in mediating preemptive analgesia[8,9].

The hormonal stress response after major surgery is well documented and includes activation of ß-endorphin and its precursors[10]. There is debate, however, about the amount of "authentic" ß-endorphin in plasma, as the conventional radioimmunoassays (RIAs) are not specific for the complete peptide[11], and even highly specific two-site RIAs still may pick up ß-endorphin derivates instead of the whole peptide. Besides ß-endorphin, cortisol has been established as a valid parameter of postoperative pain[12,13].

The aim of our study was to examine the effect of a long-lasting preemptive epidural analgesia on parameters of the hormonal stress response.

Methods

After approval of the local ethics committee and written informed consent, 42 consecutive adult patients, scheduled for total hip replacement were included into this double-blinded, randomized controlled clinical study. Exclusion criteria included contraindications for epidural anesthesia, neurologic or coagulation disorders, analgesic abuse or regular narcotic medication and an ASA-classification of 4 or higher. All routine medication, including analgesics, was continued until the evening before the operation. On the afternoon of the day preceding the operation, all patients were transferred from the general ward to the intermediate care ward of the Department of Orthopedics. After insertion of an intravenous line, all patients received an epidural catheter into the lumbar epidural space L3/4. After a test dose consisting of 10 ml ropivacaine 0.2% and confirmation of the correct position with pinprick and cold spray, patients were randomized via a computer system into one of two groups. Details of the clinical procedure have been published previously[14].

Sample

Patients in the study group ("preemptive", n = 21) then received, via a pump, a continuous infusion of ropivacaine 0.2% with a rate of 5 ml*h-1. In case of incomplete analgesia, the rate of the epidural pump was increased to a maximum of 10 ml*h-1. In case of motor blockade, the rate was reduced to a minimum of 3 ml*h-1. The study protocol planned that preemptive analgesia lasted for at least 12 hrs prior to surgery.

After confirmation of the correct epidural position, patients of the control group ("placebo", n = 21) received, via a pump, a continuous infusion of saline 0.9% with a rate of 5 ml*h-1.

All patients remained in the intermediate care unit until patients were transferred to the operating room. In both groups, the epidural application was continued until patients were transferred to the operating room. All patients received standard oral premedication with midazolam 7.5 mg. For operative analgesia, epidural ropivacaine 1% was used to achieve a sensory blockade until segment T8. Central venous, arterial and Foley catheters were inserted, as deemed appropriate by the attending anesthesiologist.

After completion of the surgical procedure, patients of both groups received a patient controlled epidural analgesia pump and were returned to the intermediate care unit. Application parameters of the pump included boluses of 5 ml ropivacaine 0.2% with a lock out interval of 15 min without an upper dose limit. In case of insufficient analgesia, patients were allowed to order a rescue analgesic consisting of intravenous piritramide. Epidural catheters were removed upon request of the patients. Patients stayed

in the intermediate care unit until the morning of the first postoperative day.

Parameters

Main outcome parameter was the time course of the plasma concentrations of ß-endorphin [1-31]. This included preoperative (change from baseline to begin of surgery) as well as postoperative (beginning after completion of surgery until removal of the epidural catheter) assessment. Additional outcome parameters were plasma concentrations of cortisol, adrenocorticotrope hormone. To assess the effect of preoperative epidural analgesia, values of visual analogue pain scales were also measured. All laboratory parameters were drawn from a central-venous catheter, after at least 10 ml had been discarded. They were collected in EDTA-filled devices, stored until centrifugation, in cooled systems, and then frozen to –80° C. Blood plasma samples were further processed after a maximum time of 6 weeks. Special proceedings for detection of ß-endorphin have been described earlier[15]. Briefly summarized, this highly specific assay is a two-site fluid phase immunoprecipitation RIA. The intra-assay coefficient of variation is 3.7%, and the inter-assay coefficient of variation is 3.8%. There are no cross-reactivities for incomplete parts of the ß-endorphin peptide, or for acetyl-N-ß-endorphin.

Points of measurement

All measurements were taken before insertion of the epidural catheter on the day before operation (M1), on arrival in the operating room (M2), after completion of surgery (M3), four hours after completion of surgery (M4), on the evening of the operating day (M5), and on every morning and evening until the epidural catheter was removed (M6-11).

Statistics

Statistical evaluation was achieved with analysis of variance for biometric, anesthesia, and operation related data. All other parameters were tested with multifactorial analysis of variance. In case of parameters not showing normal distribution, further calculation was done with log values. Results were considered statistically significant if p-value was below 0.05.

Results

Both groups were comparable regarding biometric, operation- and anesthesia related data. However, there was a trend towards younger age in the "preemptive" group (57±12 vs. 65±6 years, Table 1).

At the time of inclusion, chronic therapy with non-steroid analgesics was performed in 12 ("preemptive") and 9 (control) patients (non-significant). Preoperatively, epidural analgesia was performed in both groups for 11-20 hrs. Preemptive analgesia proved to be very effective, as visual analogue pain scale ratings decreased in study patients significantly.

Table 1
Biometric, operation and anesthesia related data. Given are mean values and standard deviations. For VAS values, ranges are given additionally. NSAID= non-steroid anti-inflammatory drugs, ASA= American Society of Anesthesiologists, VAS= visual analogue pain scale.

	Preemptive (n=21)	Placebo (n=21)	
Gender (% female)	66	70	p=1
Age (years)	65 (6)	57 (12)	p=0.08
Height (cm)	166 (6)	165 (8)	p=0.676
Weight (kg)	79 (12)	78 (18)	p=0.839
ASA-classification			p=0.766
I	3	3	
II	15	16	
III	3	2	
Duration of operation (min)	107 (30)	105 (22)	p=0.92
Midazolam (mg)	10.3 (2.5)	10.9 (3.3)	p=0.664
Need for general anesthesia	3	3	p=1
Propofol (mg)	263 (269)	264 (229)	p=0.87
VAS before "preemptive" analgesia (M1)	30.7 (5-72)	32.1 (10-64)	n.s.
VAS after "preemptive" analgesia (M2)	6.2 (0-20)	31.2 (5-78)	p<0.001
VAS M3	1 (0-20)	0	
VAS M4	38.4 (20-60)	39.9 (10-68)	
VAS M5	35 (5-55)	44.2 (10-72)	
VAS M6	29 (10-50)	38.4 (15-86)	
VAS M7	22.2 (10-45)	23.6 (5-52)	
VAS M8	11.7 (0-40)	13.8 (0-35)	
VAS M9	15 (0-32)	9.1 (5-20)	
VAS M10	16.7 (5-22)	5 (2-8)	

In contrast, VAS values remained constant in the control group (Table 1). Throughout the study period, VAS values were comparable in both groups with a trend to lower values in the study group (Table 1).

Epidural anesthesia was sufficient for surgical block in all cases. However, in both groups there were three patients who required general anesthesia with laryngeal mask because of restlessness in spite of sufficient analgesia. In these cases only propofol and no opioids were used intraoperatively.

Table 2
Plasma concentrations of ß-endorphin [1-31] in pmol/l. Given are median values and ranges. No statistically significant differences between study groups were observed.

	Preemptive (n=21)	Placebo (n=21)	
ß-endorphin M1	0 [0-20.6]	0 [0-24.0]	n.s.
ß-endorphin M2	7.0 [0-24.1]	7.9 [0-23.1]	n.s.
ß-endorphin M3	0 [0-22.4]	0 [0-17.1]	n.s.
ß-endorphin M4	0 [0-16.5]	0 [0-25.3]	n.s.
ß-endorphin M5	0 [0-36.3]	0 [0-26.8]	n.s.
ß-endorphin M6	0 [0-12.3]	0 [0-27.0]	n.s.
ß-endorphin M7	0 [0-17.4]	0 [0-22.0]	n.s.
ß-endorphin M8	0 [0-19.8]	0 [0-20.8]	n.s.
ß-endorphin M9	0 [0-15.7]	0 [0-31.9]	n.s.
ß-endorphin M10	0 [0-10.4]	0 [0-0]	n.s.

Table 3
Plasma concentrations of adrenocorticotrope hormone (ACTH) in pg/l. Given are median values and ranges. No statistically significant changes were observed.

	Preemptive (n=21)	Placebo (n=21)	
ACTH M1	27.0 [1.6-152.4]	20.7 [3.9-968.1]	n.s.
ACTH M2	32.6 [3.6-253.2]	44.3 [4.9-358.5]	n.s.
ACTH M3	24.9 [4.0-294.9]	27.2 [3.0-267.4]	n.s.
ACTH M4	66.0 [16.5-261.8]	35.9 [3.9-137.8]	n.s.
ACTH M5	25.5 [3.0-1167.7]	27.8 [2.6-682.6]	n.s.
ACTH M6	12.4 [3.5-180.6]	8.8 [3.6-107.1]	n.s.
ACTH M7	13.1 [1.1-52.8]	7.8 [2.6-33.3]	n.s.
ACTH M8	12.5 [1.7-172.4]	13.2 [4.0-27.8]	n.s.
ACTH M9	9.9 [5.7-69.1]	11.4 [2.5-18.5]	n.s.
ACTH M10	8.6 [4.5-48.9]	7.2 [6.9-7.4]	n.s.

Preemptive analgesia did not lead to significant changes in the plasma concentrations of ACTH or ß-endorphin as compared to baseline values before the start of epidural analgesia. Concentrations of ß-endorphin [1-31] peaked in both groups before surgery (M2), declined until the evening of the operation day, and again rose to an elevated level where they stayed until the end of the study. There were no significant differences between both groups. Plasma concentrations of ACTH remained elevated from the end of surgery (M3) to the evening of the operation day (M5). Thereafter, values declined to normal without significant differences between groups (Tables 2 and 3).

In contrast, cortisol concentrations remained stable throughout the preoperative period in the "preemptive" group, whereas they rose significantly in the control group ($p = 0.015$). However, in the period after surgery, no intergroup differences could be detected (Table 4).

Table 4: Plasma concentrations of cortisol (median values and ranges) in pg/l. There was a significant increase in the control group from the preoperative day to the morning of surgery in the control group, whereas values remained stable in the "preemptive" group. Subsequently, no significant changes occurred.

	Preemptive (n=21)	Placebo (n=
Cortisol M1	12.4 [2.3-41.3]	11.6 [1.6-4
Cortisol M2	14.9 [5.6-36.4]	25.0 [1.3-1
Cortisol M3	13.5 [2.5-734.8]	15.5 [6.7-10
Cortisol M4	38.4 [9.6-115.9]	28.3 [11.1-1
Cortisol M5	22.9 [8.4-179.6]	25.1 [13.1-1
Cortisol M6	19.1 [5.1-84.4]	20.7 [3.2-4
Cortisol M7	14.9 [7.2-34.5]	14.2 [3.1-3

Discussion

The idea of a preempting pain before it starts has been proposed very early [16]. In more recent times, the phenomenon of hyperexcitability has attracted attention[17] and has led to new interest in "preemptive analgesia"[18]. However, the concept has been challenged, as study results were inconsistent. Part of this inconsistency may be due to terminology, as not all studies on preemptive analgesia really investigated this phenomenon[19]. The term only strictly applies, if analgesia is started in advance and continues into the postoperative period[20]. According to this definition our study investigated preemptive analgesia.

The way in which preemptive analgesia may work has not been established yet. However, there is evidence that neuronal hyperexcitability plays a pivotal role in triggering chronic pain[21]. This may be mediated by upregulation of sensory neuron-specific

sodium channels and vanilloid receptors, phenotypic switching of large myelinated axons, sprouting within the dorsal horn, and loss of inhibitory neurons due to apoptotic cell death[22]. If preemptive analgesia offers a clinically relevant benefit for patients, this may be through inhibition of one or more of these effects. It was the rationale of our study to establish preemptive analgesia by the blocking of sensory input at the spinal cord level via an epidural block for a substantial time before surgery. This led, as our study results show, to a decrease in pain perceived in the hip operated on.

Endogenous opioids are reported to be an important part of the human stress response to surgery or inflammation[23,24] and thus may play a major role in the emergence of chronic pain. In studies of anginal pain, correlations between pain and ß-endorphin values have been found, suggesting a pivotal role of ß-endorphin in acute pain states[25]. Hence, in our study, we investigated the plasma concentrations of ß-endorphin [1-31], cortisol, and ACTH. In numerous patients, we could detect very small amounts of ß-endorphin, which did however not follow a specific reproducible pattern. In contrast, mean peak concentrations of cortisol ran parallel with pain ratings, as measured by the visual analogue pain scales. Maximum VAS values and maximum cortisol concentrations were observed four hours after completion of surgery (M4, preemptive group) or on the evening of the day of operation (M5, control group). In our study, however, we were unable to detect a correlation between ß-endorphin concentrations and varying VAS values. Furthermore, in spite of the fact that preemptive analgesia proved to be highly effective, as measured by suppressed VAS values in the "preemptive group" before surgery, this did not lead to a suppression of ß-endorphin into the circulation. Additionally, "preemptive analgesia" led to a decreased consumption of postoperative analgesics, which further corroborates the fact that this procedure may be effective[14]. However, effective "preemptive analgesia" did not lead to an effect upon ß-endorphin concentrations. This lack of an effect might be explained by different mechanisms. In the first place, ß-endorphin might not be suitable as a predictor of chronic pain because of rapid elimination out of the plasma[26]. Furthermore the plasmatic compartment might not be the right place to detect an effect in endogenous opioid biology[24,27]. Thirdly, the preemptive effect of epidural ropivacaine might not have been sufficient to produce a sustainable effect upon stress markers. A fourth explanation might be that the role of ß-endorphin, for describing postoperative pain states, may have been exaggerated. Possibly the peptide plays an important part in the human stress response, but is not specifically linked to varying pain states.

In contrast to most other studies on "preemptive analgesia"[1], our study was the first to establish long-lasting (14 hrs median) epidural analgesia in the presence of chronic pain. Thus if ß-endorphin plays a role in the assessment of pain, our study does not give conclusive results what pain-free time interval might be required to produce a significant effect upon ß-endorphins.

In conclusion, this study shows that long-lasting preoperative epidural analgesia with ropivacaine in the presence of pain, leads to a significant reduction in pain levels and plasmatic cortisol concentrations, but does not have an effect on plasma concentrations of beta-endorphin [1-31] or ACTH.

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