Pre-incisional epidural ropivacaine, sufentanil, clonidine, and (S)-+ketamine does not provide pre-emptive analgesia in patients undergoing major pancreatic surgery


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Background. The concept of pre-emptive analgesia remains controversial. This prospective, randomized, and double-blind study compared epidural administration of ropivacaine 2 mg ml⁻¹, sufentanil 0.5 μg ml⁻¹, clonidine 3 μg ml⁻¹, and (S)+ketamine 0.25 mg ml⁻¹ (study solution) given before incision with the same combination started at the end of the operation.

Methods. After testing the stability of the solution using high performance liquid chromatography (HPLC) and examining 12 patients for possible side-effects in comparison with the epidural infusion of ropivacaine 2 mg ml⁻¹ and sufentanil 0.5 μg ml⁻¹, 30 patients undergoing major pancreatic surgery were recruited into the study. Before induction of anaesthesia, an epidural catheter was inserted (TH6–8). Patients in Group 1 received a bolus of 8 ml followed by a continuous infusion (8 ml h⁻¹) of the study solution before induction of anaesthesia. In Group 2, patients received the same volume of saline before operation, the study solution was started at the end of surgery. After operation, the infusion was maintained for at least 96 h using a patient-controlled epidural analgesia (PCEA) pump in both groups. Patients were evaluated up to the seventh postoperative day for pain and side-effects.

Results. Visual analogue scale (VAS) values at rest were as follows: G1 vs G2: 24 h, 19 (SD 23) vs 6 (13); 48 h, 4 (10) vs 11 (21); and 72 h, 12 (22) vs 13 (21). VAS values during coughing and mobilization were also comparable. Total volume of epidural infusion was 904 (114) ml in G1 vs 892 (154) ml in G2. The incidence of side-effects (nausea, vomiting, and motor block) was low and not different between the groups.

Conclusions. Pre-incisional epidural analgesic infusion did not provide pre-emptive analgesia compared with administration started at the same time point of operation, but both groups had low pain scores.

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The management of pain still remains a major concern in the perioperative period,1 not only because pain affects surgical outcome,2 but postoperative pain also may result in the development of chronic pain even after minor surgery.3 Since the original suggestion4 5 that pre-emptive analgesic treatment should reduce the intensity of postoperative pain and the development of central...

Results of this study were presented, in part, at meetings of the European Society of Regional Anaesthesia (ESRA) in Athens 2004 and in Monaco 2006, and at the meetings of the German Society of Anaesthesiology in Nuernberg 2004 and in Leipzig 2006.

Declaration of interest. The study was carried out at the Department of Anaesthesiology, University Hospital Hamburg Eppendorf, and received financial support from AstraZeneca, Wedel, Germany. This consisted of payment of the local ethics committee fee and insurance for the patients.
hypersensitivity and the incidence of hyperalgesia, many clinical and experimental studies have been performed to explore this hypothesis. Although a number of studies in animals demonstrated that some anti-nociceptive techniques given before the pain stimulus were able to reduce the intensity of pain compared with using the same technique after injury, the results of early clinical studies were mostly disappointing. 

A recent review of clinical studies analysed the effect on pain during the first 24 h of starting analgesia before operation compared with after operation. The authors concluded that there was no beneficial effect of pre-emptive analgesia on postoperative pain. They proposed that the effect of prolonged and intensive multimodal analgesic interventions should be compared with less aggressive conventional perioperative analgesia. However, one study has shown a pre-emptive effect of epidural analgesia but not of other analgesia techniques.

We have performed a prospective, randomized, double-blind, and placebo-controlled study to evaluate if starting a combined epidural infusion of ropivacaine, sufentanil, clonidine, and S(+) -ketamine before surgery provides pre-emptive analgesia when compared with starting the same solution at the end of the operation.

Methods
The study was divided into two parts:
(i) Part I: testing the stability and the side-effects of the study solution.
(ii) Part II (main study): evaluation of the pre-emptive analgesic effects of epidural anaesthesia using the study solution at two different start points.

Part I
The study solution consisted of ropivacaine 2 mg ml\(^{-1}\), sufentanil 0.5 \( \mu \text{g ml}^{-1}\), clonidine 3 \( \mu \text{g ml}^{-1}\), and S(+) -ketamine 0.25 mg ml\(^{-1}\). Before starting the patient study, we evaluated the stability of the solution, including measurement of the pH. After preparation by the staff pharmacist, the solution was stored at room temperature. A part of the solution was withdrawn from the plastic bag for measurement of the pH-value every day during a period of 10 days.

The stability of the various drugs in the study solution was measured with high performance liquid chromatography (HPLC) from samples taken on days 1, 2, 3, 10, and 26 after preparation using fentanyl as an internal standard, in the Department of Forensic Medicine. Study solution was stored in a fridge at 8°C. A ratio of the internal standard and the respective analyte [ropivacaine, sufentanil, clonidine, and S(+) -ketamine] was calculated for each HPLC run. The relative standard deviation of all the measurements of each analyte was calculated.

The potential side-effects of the study solution were evaluated in comparison with the epidural solution we routinely use for postoperative epidural pain management in our hospital (ropivacaine 2 mg ml\(^{-1}\) and sufentanil 0.5 \( \mu \text{g ml}^{-1}\)) in a double-blind, prospective, and randomized manner. After approval of the local ethics committee and written informed consent, 12 patients undergoing major pancreatic surgery were included in this part of the study.

On the day of surgery, patients received oral premedication with 0.1 mg kg\(^{-1}\) midazolam (Hoffmann LaRoche, Grenzach-Wyhlen, Germany). A venous line was inserted and infusion of 500 ml Ringer’s solution was started. Before induction of anaesthesia, an epidural catheter was introduced in the sitting position at T7/8 using the loss of resistance technique. After a test dose (lidocaine 2.5 ml, 1%, AstraZeneca, Wedel, Germany), the catheters were tunnelled s.c. and secured with a single stitch. Within 10 min after the test dose, a bolus of 8 ml of the respective study solution was given in a double-blind manner. Study medication was delivered by the hospitals’ pharmacy department in 300 ml bags containing one of the solutions. Using a computerized randomization list, the pharmacist filled the bags with 300 ml of either ropivacaine 2 mg ml\(^{-1}\) (AstraZeneca) and sufentanil 0.5 \( \mu \text{g ml}^{-1}\) (Janssen-Cilag, Neuss, Germany) or ropivacaine 2 mg ml\(^{-1}\), sufentanil 0.5 \( \mu \text{g ml}^{-1}\), clonidine 3 \( \mu \text{g ml}^{-1}\), and S(+) -ketamine 0.25 mg ml\(^{-1}\) under sterile conditions. The bags for both study groups appeared identical. A closed envelope with information about the patients’ study medication was added in the patients’ record for emergency cases. Other than the pharmacist, everyone involved in the study was blinded to the medication.

After the bolus dose, anaesthesia was induced with sufentanil 0.5 \( \mu \text{g kg}^{-1}\) (Janssen-Cilag) and 2 mg kg\(^{-1}\) propofol (AstraZeneca). Endotracheal intubation was facilitated with rocuronium bromide 0.5 \( \mu \text{g kg}^{-1}\) (Organon, Oberschleißheim, Germany). Maintenance of anaesthesia was with sufentanil 0.1 \( \mu \text{g kg}^{-1}\) and isoflurane 0.7–1.0 vol.% with an inhaled F\(_{I\text{O}}\)\(_2\) of 0.3 in air. Normothermia was maintained with forced air. Additional monitoring included a jugular venous line for central venous blood gas measurement, a radial arterial line for arterial pressure and a urinary catheter. During surgery, the epidural infusion was given at 8 ml h\(^{-1}\). At the end of the operation, patients were awakened and transferred to the post-anaesthesia care unit (PACU). Continuous infusion of the epidural solution was interrupted and a patient-controlled epidural analgesia (PCEA) pump (Pegasus light\(^{\circ}\), Logomed, Kiel, Germany) was connected to the epidural catheter (continuous infusion rate: 8 ml h\(^{-1}\), bolus: 2 ml, lock-out time: 15 min). The patients were transferred to the intermediate care (IMC) unit for one night before going back to the ward. PCEA of the study solutions was maintained until postoperative day 4. From day 2, the infusion rate could be adjusted to the needs of the patient.
Haemodynamic variables (heart rate and arterial pressure) were measured before operation, 1 and 4 h after start of the operation, on arrival and after 6.5 h in PACU, and in the morning on the following 4 days. Pain scores using the visual analogue scale (VAS) (0–100: 0, no pain; 100, maximum imaginable pain) were evaluated at rest and during coughing on arrival and after 6.5 h in PACU, and in the morning on the following 4 days. Side-effects such as shivering, postoperative nausea and vomiting, and intensity of motor blockade using the Bromage scale (0–3) were assessed. Sedation was evaluated using the following sedation score: 1, patient awake; 2, patient easy to awake; 3, patient difficult to awake; 4, patient impossible to awake.

Part II

In the second part of the study, the pre-emptive effects of the study solution containing ropivacaine, sufentanil, clonidine, and $S(\pm)$-ketamine were evaluated after approval of the local ethics committee and written informed consent. Thirty adult patients undergoing major pancreatic surgery were included in the study. Patients with pre-existing pain (VAS $>$ 10) or with regular intake of analgesics were excluded from the study.

Placement of epidural catheters, management of anaesthesia, and preparation of the study solution were performed as described in Part I. Using a computerized randomization, patients were allocated in a double-blind manner to receive either an initial bolus of 8 ml of the study solution in Group 1 (G1) or the same volume of saline in Group 2 (G2) after placement of the epidural catheter and before induction of anaesthesia. After induction of anaesthesia, the epidural infusion (G1: ropivacaine, sufentanil, clonidine, and $S(\pm)$-ketamine; G2: saline) was maintained at 8 ml h$^{-1}$ by continuous infusion. Intraoperatively, hypotension was treated with i.v. fluids (HES 130/0.4) or continuous low-dose norepinephrine. The epidural infusion was maintained until 30 min before end of surgery. At this time, patients in G1 received a bolus of 8 ml of saline, and patients in G2 received a bolus of 8 ml of ropivacaine 2 mg ml$^{-1}$, sufentanil 0.5 $\mu$g ml$^{-1}$, clonidine 3 $\mu$g ml$^{-1}$, and $S(\pm)$-ketamine 0.25 mg ml$^{-1}$. After this bolus, a PCEA pump (Pegasus light$^\text{TM}$) was connected to the epidural catheter. Both groups received the study mixture with a continuous infusion rate of 8 ml h$^{-1}$ and a bolus dose of 2 ml with a lock-out time of 15 min. The continuous infusion rate of the study solution could be adjusted to the need of each patient on the first postoperative day. After the operation, patients were awakened and transferred to the PACU. If the epidural analgesia was insufficient, the patient would be withdrawn from the study. Patients stayed in the PACU at least 4 h before being transferred to the intermediate care unit (IMC) for 1 day. Afterwards, patients were treated on the peripheral ward. Patients additionally received $3 \times 1$ g of novaminsulfone i.v., which has analgetic, anti-inflammatory, and antipyretic properties, for at least 3 days.

After operation, patients were visited 2 and 4 h after surgery and in the morning and evening until the seventh day after surgery. During these visits, patients were evaluated with respect to pain intensity (see Part I) at rest, and during coughing. VAS values were evaluated during mobilization (standing in front of the bed). The cumulative amount of epidural infusion, side-effects of pain therapy, Bromage scale, and haemodynamic variables were evaluated during every visit.

Three months after surgery, patients were contacted by phone to be interviewed with respect to pain intensity (at rest, during coughing, and mobilization) and possible side-effects.

Statistics

Computerized statistical analysis was performed using the program SPSS 9.0 (SPSS Inc., Chicago, IL, USA). The power analysis of the study was performed, as previously described,$^{11}$ using the cumulative consumption of administered study solution at 96 h. We set 8 ml h$^{-1}$ as the mean dose of analgesic required epidurally, resulting in a cumulative dose of 768 ml in 96 h. For calculation of sample size, we decided the smallest difference to be statistically significant was 15% (105 ml) of the cumulative amount of epidural analgesics over 3 days. The anticipated standard deviation was set at 80 ml of the cumulative dose. We would permit a type I error of $\alpha=0.05$, and with the alternate hypothesis, the null hypothesis would be retained with a type II error of $\beta=0.2$. This reaches a power of 0.8 and indicated that a sample size of at least 14 patients per group was necessary.

Differences between the groups were compared using the unpaired Student’s $t$-test (demographic and perioperative data). VAS values were tested using the Mann–Whitney $U$-test. Incidences of side-effects were compared using the $\chi^2$ test. Analysis was corrected for repetitive testing at multiple time points. Data are expressed as mean (SD) or incidences if not otherwise declared. $P<0.05$ was considered to be statistically significant.

Results

Part I

Measurement of the pH resulted in stable values until day 10, day 1 4.89, and on the 10th day 4.59. The mean pH value was 4.75 (0.1) (range 4.59–4.89). The components of the study solution remained stable up to 26 days (Table 1). Differences between the measurements are within the variability of the measurement technique.

The incidence of side-effects in patients receiving the study solution when compared with the standard epidural

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infusion showed no difference between the groups (Table 2). The haemodynamic variables were within the normal range and did not show differences between the groups. Values at rest were as follows: Group R/S vs Group R/S/C/K: arrival PACU: 26 (39) vs 3 (8); 6.5 h PACU: 25 (17) vs 10 (14); 24 h: 23 (27) vs 18 (21); 48 h: 12 (11) vs 10 (17); 72 h: 0 (0) vs 8 (13); 96 h: 13 (21) vs 5 (15). During coughing VAS values developed as follows: Group R/S vs Group R/S/C/K: 6.5 h PACU: 35 (25) vs 10 (14); 24 h: 35 (24) vs 30 (28); 48 h: 26 (30) vs 22 (29); 72 h: 18 (30) vs 20 (23); 96 h: 30 (21) vs 13 (15). No significant differences with respect to pain scores could be detected between the groups. The cumulative amount of the respective study solution was (Group R/S vs Group R/S/C/K) after 6.5 h PACU: 111 (15) vs 115 (5) ml; 24 h: 224 (22) vs 198 (19) ml; 48 h: 433 (63) vs 409 (49) ml; 72 h: 617 (61) vs 615 (89) ml; 96 h: 800 (81) vs 725 (62) ml.

No relevant side-effects could be detected in both groups. In PACU, two patients in Group R/S and one patient in Group R/S/C/K had shivering. Only one patient, in Group R/S/C/K, had nausea 72 h after surgery. No patient had any motor blockade. One patient in Group R/S/C/K collapsed 1 day after surgery due to orthostatic hypotension during walking to the toilet. One patient in Group R/S/C/K was difficult to awake 6.5 h after surgery (sedation score 3). At all other evaluations, patients were awake or easy to awake (sedation score 1 or 2). No differences between the groups could be detected.

**Part II**

Three patients were excluded from statistical analysis (one patient, in G1, due to accidental removal of the epidural catheter within 24 h, and in G2, one had revision surgery on the first night and the second patient only had a gastroenterostomy).

Epidural analgesia was effective and sufficient in all patients (Table 2). Intraoperative sufentanil i.v. showed a trend to a lower amount in G1 (P=0.058). Nine patients in G1 and 10 patients in G2 underwent a Whipple’s procedure; all the other patients underwent other major pancreatic surgery such as pancreatectomy with or without duodenectomy and resection of the tail of the pancreas. Surgical incision was the same in all patients. All patients in both groups could be extubated directly after surgery and were transferred to the IMC Unit after remaining in the PACU for 4 h.

Up to postoperative day 7, VAS values were comparable between the groups at rest, on coughing, and during mobilization at each time of evaluation (Figs 1–3). The only significant difference could be demonstrated 4 h after surgery when VAS values in G2 were significantly lower compared with those of G1. VAS values 3 months after surgery were low in both groups (Figs 1–3).

The cumulative amount of study solution via the PCEA pump did not differ between the groups (Table 3).

The haemodynamic variables remained stable during the study period. No norepinephrine had to be given in the postoperative period. The incidence of side-effects like nausea, vomiting, and shivering was low and comparable between the groups.

### Table 1
**Ratio of internal standard using fentanyl as the respective analyte**

<table>
<thead>
<tr>
<th></th>
<th>Clonidine</th>
<th>S(+)-ketamine</th>
<th>Ropivacaine</th>
<th>Sufentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.21</td>
<td>56.1</td>
<td>538</td>
<td>0.17</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.22</td>
<td>52.4</td>
<td>471</td>
<td>0.17</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.22</td>
<td>53.2</td>
<td>439</td>
<td>0.18</td>
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<tr>
<td>Day 10</td>
<td>0.19</td>
<td>49.1</td>
<td>432</td>
<td>0.17</td>
</tr>
<tr>
<td>Day 26</td>
<td>0.24</td>
<td>62.2</td>
<td>480</td>
<td>0.17</td>
</tr>
<tr>
<td>Mean</td>
<td>0.22</td>
<td>54.6</td>
<td>472</td>
<td>0.17</td>
</tr>
<tr>
<td>Rel. sd</td>
<td>8.3%</td>
<td>9.1%</td>
<td>9.0%</td>
<td>2.6%</td>
</tr>
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</table>

### Table 2
**Patient and perioperative data presented as mean (range) or mean (SD)**

<table>
<thead>
<tr>
<th></th>
<th>Group R/S (n=6)</th>
<th>Group R/S/C/K (n=6)</th>
<th>P-value</th>
</tr>
</thead>
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<tr>
<td>Age (yr)</td>
<td>45 (27–60)</td>
<td>52 (32–68)</td>
<td>0.37</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181 (5)</td>
<td>176 (7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (7)</td>
<td>80 (12)</td>
<td>0.7</td>
</tr>
<tr>
<td>ASA status (I/II/III)</td>
<td>1/50</td>
<td>0/60</td>
<td>0.9</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>303 (37)</td>
<td>350 (36)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sufentanil intraop (µg)</td>
<td>75 (25)</td>
<td>63 (12)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Group Preop (n=14)</th>
<th>Group Postop (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>56.6 (37–77)</td>
<td>53 (28–69)</td>
<td>0.44</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.5 (13)</td>
<td>67.8 (13)</td>
<td>0.43</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 (10)</td>
<td>175 (7)</td>
<td>0.48</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>0/13/1</td>
<td>0/13/0</td>
<td>0.3</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>355 (111)</td>
<td>331 (101)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

**Fig 1** VAS values at rest (mm) (*P<0.05). 2 h postop, 2 h after surgery; 4 h postop, 4 h after surgery; POD 1/1, postoperative day 1/evaluation 1 (in the morning); POD1/2, postoperative day 1/evaluation 2 (in the evening) etc.; 3 months, VAS values 3 months after surgery.
Discussion

Continuous perioperative infusion of an epidural combination of ropivacaine, sufentanil, clonidine, and S(+)‐ketamine did not provide pre‐emptive analgesia. Our study was based on a review suggesting that the best approach to provide pre‐emptive analgesia could be by giving a combination of different analgesic agents which work on a different part of the pain pathway. Each of the analgesic agents we used acted on a different part of the pathway. Local anaesthesia blocks the transmission of pain, ketamine, sufentanil, and clonidine provide spinal modulation of pain, and sufentanil and clonidine act on the perception of pain. However, our regimen was not able to provide pre‐emptive analgesia. We are not able to exclude a partial pre‐emptive effect by the perioperative use of sufentanil in G2.

In our study, pre‐emptive analgesia was defined as treatment initiated before the surgical incision in comparison with the same regime started after operation, as has been used previously. After promising findings in animal studies, the results of clinical studies using this design have been disappointing. Systematic reviews of pre‐emptive analgesia concluded that pre‐injury or post‐injury initiation of analgesia has no significant impact on postoperative pain relief.

In contrast, a recent meta‐analysis covering studies from 1987 to 2003 and measuring the outcome variables, pain intensity score during the first 24–48 h, total supplemental postoperative analgesic requirements, and time to first rescue analgesic, concluded that pre‐emptive epidural analgesia resulted in an improvement of all three outcome variables, but wound infiltration with local anaesthetics, systemic non‐steroidal anti‐inflammatory drugs (NSAIDs), N‐methyl‐d‐aspartate (NMDA) receptor antagonists and opioids failed to provide pre‐emptive analgesia. The differences between the different meta‐analyses may be the result of additional studies published between 2001 and 2003 being included with stricter criteria of inclusion and some older studies not being included.

To our knowledge, our study is the first study evaluating the pre‐emptive effects of a combination of the four agents, ropivacaine, sufentanil, clonidine, and S(+)‐ketamine given epidurally with the infusion continued for at least 72 h after operation. These four agents have already been used in previous studies, but the ketamine was administered i.v. One study failed to show pre‐emptive analgesia with a single preoperative dose of morphine, clonidine, and ketamine i.v. in patients undergoing transperitoneal tumour nephrectomy, compared with the postoperative administration of the same drugs. Effective pre‐emptive analgesia was achieved in patients undergoing major bowel surgery by a bolus dose of ketamine 0.5 mg kg⁻¹ i.v. before operation, followed by a continuous i.v. infusion of 0.25 mg kg⁻¹ h⁻¹ intraoperatively in combination with intra‐ and postoperative epidural bupivacaine, sufentanil, and clonidine. This infusion regime was superior to a postoperative regime using lidocaine, morphine, and clonidine.

In agreement with the previously published data, we conclude that timing of analgesia seems not to play the major role in the reduction of postoperative pain scores and probably the prevention of the development of chronic pain.

![Fig 2 VAS values during coughing (mm). 2 h postop, 2 h after surgery; 4 h postop, 4 h after surgery; POD 1/1, postoperative day 1/evaluation 1 (in the morning); POD1/2, postoperative day 1/evaluation 2 (in the evening) etc.; 3 months, VAS values 3 months after surgery.](image1)

![Fig 3 VAS values during mobilization (mm). 2 h postop, 2 h after surgery; 4 h postop, 4 h after surgery; POD 1/1, postoperative day 1/evaluation 1 (in the morning); POD1/2, postoperative day 1/evaluation 2 (in the evening) etc.; 3 months, VAS values 3 months after surgery.](image2)

<table>
<thead>
<tr>
<th>Group Preop.</th>
<th>Group Postop.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 h postop (ml)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>4 h postop (ml)</td>
<td>43 (7)</td>
</tr>
<tr>
<td>POD 1/1 (ml)</td>
<td>148 (29)</td>
</tr>
<tr>
<td>POD 1/2 (ml)</td>
<td>241 (29)</td>
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<td>POD 2/1 (ml)</td>
<td>347 (57)</td>
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<tr>
<td>POD 2/2 (ml)</td>
<td>442 (75)</td>
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<td>POD 3/1 (ml)</td>
<td>548 (92)</td>
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<td>POD 3/2 (ml)</td>
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<td>POD 4/1 (ml)</td>
<td>715 (101)</td>
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<tr>
<td>POD 4/2 (ml)</td>
<td>780 (105)</td>
</tr>
<tr>
<td>POD 5/1 (ml)</td>
<td>853 (108)</td>
</tr>
<tr>
<td>POD 5/2 (ml)</td>
<td>914 (114)</td>
</tr>
</tbody>
</table>

Table 3 Cumulative volume of study solution administered (POD 1/1, postoperative day 1/first evaluation in the morning; POD 1/2, postoperative day 1/second evaluation in the evening)
syndromes. Pogatzki-Zahn and Zahn recently suggested that the extension of a multimodal analgesic treatment into the postoperative period may be superior to pre-emptive analgesia. The concept of ‘preventive analgesia’ includes the administration of an appropriate combination and concentration of different analgesics and their extension into the postoperative period. It is obviously important to evaluate the duration and efficacy of any perioperative analgesic intervention to reduce postoperative pain and to prevent the development of chronic pain syndromes. This includes the evaluation of different drugs such as oral gabapentin or epidural neostigmine. To evaluate the preventive effects of the combination used in our present study, it may be useful to compare it with ropivacaine/sufentanil combination we used in Part I. The evaluation of pain scores was not part of this study, and the number of patients was too low to effectively compare the pain scores, but our study solution was able to provide relatively low pain scores in patients undergoing major pancreatic surgery. It is possible that the dose of the drugs in our study was too low as we used analgesic, but not anaesthetic doses. Therefore, it is possible that we were not able to block the nociceptive input from the surgical area and this may explain the failure of the pre-emptive technique.

In conclusion, the pre-emptive and extended administration of a combination of sufentanil, ropivacaine, clonidine, and S(+)-ketamine epidurally did not result in a reduction in postoperative pain scores. However, pain scores in both study groups were very low indicating excellent pain relief. Further evaluation of the effects of the combination in different concentrations and in comparison with other drug combinations is warranted.

Funding
The study received financial support from AstraZeneca, Wedel, Germany. This consisted of payment of local ethics committee fee and insurance for the patients.

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