Anesthesiology 2002; 97:952–8

Postoperative Wound Oxygen Tension with Epidural or Intravenous Analgesia

A Prospective, Randomized, Single-blind Clinical Trial

Donal J. Buggy, M.D., M.Sc., F.R.C.P.I., F.C.A.R.C.S.I., F.R.C.A., Warren L. Doherty, F.R.C.A.,† Elaine M. Hart, F.R.C.A.,† Edward J. Pallett, Ph.D.‡*

Background: **Adequate tissue oxygen tension is an essential requirement for surgical-wound healing. The authors tested the hypothesis that epidural anesthesia and analgesia increases wound tissue oxygen tension compared with intravenous morphine analgesia.**

Methods: **In a prospective, randomized, blind clinical study, the authors allocated patients having major abdominal surgery (n = 32) to receive combined general and epidural anesthesia with postoperative patient-controlled epidural analgesia (epidural group, n = 16), or general anesthesia alone with postoperative patient-controlled intravenous analgesia (intravenous group, n = 16). An oxygen sensor and a temperature sensor were placed subcutaneously in the wound before closure. Wound oxygen tension (P_wO_2) and temperature were measured continuously for 24 h. Other variables affecting wound tissue oxygenation and visual analogue scale (VAS) pain scores were also documented.**

Results: **Despite epidural patients having lower body temperatures at the end of surgery (35.7 ± 0.3) *versus* 36.3 ± 0.5 °C, $P = 0.004$), they had significantly higher mean P_wO_2 over the 24 h period, compared with the intravenous group (64.4 ± 14 *vs.* 50.7 ± 15) mmHg, mean (SD), 95% CI difference, −22 to −5, $P = 0.002$). Area under the P_wO_2 −24 h time curve was also significantly higher in the epidural group (930 ± 278 *vs.* 749 ± 257) mmHg × h, 95% CI difference −344 to −18, $P = 0.03$). VAS pain scores at rest and moving were significantly lower in the epidural group at all times.**

Conclusion: **Epidural anesthesia and postoperative analgesia for major abdominal surgery increases wound tissue oxygen tension compared with general anesthesia and intravenous morphine analgesia.**

DELAY or failure of healing of surgical wounds, usually a result of infection, is one of the commonest causes of postoperative morbidity, long hospital stays, and increased costs. The incidence of wound infection in patients undergoing colorectal surgery ranges from 9–27%.[1] Successful surgical wound healing requires resistance to infection, which depends mainly on oxidative killing by neutrophils. Tissue oxygen tension (P_TO_2) is an especially important determinant of postoperative wound healing, because the bactericidal ability of neutrophils is directly related to P_TO_2.[2] Moreover, P_TO_2 also influences collagen deposition, which reflects wound tensile strength.[3] Indeed, the incidence of surgical wound infection is dependent on wound tissue oxygen tension (P_wO_2).[4] Supra-normal arterial oxygen tension levels, achieved by administering supplemental perioperative oxygen, have been demonstrated to halve the incidence of surgical wound infection from 11% to 5%.[5]

Emerging evidence demonstrates that many other features of perioperative care in addition to surgical issues are influential in promoting postoperative wound healing.[6] Surgery and postoperative pain evoke profound neuroendocrine and cytokine activity known as the stress response.[7] Consequent activation of the sympathetic nervous system may evoke arteriolar vasoconstriction, reducing tissue perfusion and P_TO_2. Postoperative pain may influence tissue perfusion and oxygenation, and hence postoperative wound infection. It has recently been shown that P_TO_2 was higher in patients with superior postoperative pain relief, implying that poorly controlled surgical pain reduces tissue oxygen levels sufficiently to significantly increase the risk of surgical wound infection[8] This study measured P_TO_2 in the arm, in patients undergoing knee surgery, and subcutaneous tissue oxygen tension was presumed to reflect wound tissue subcutaneous oxygen tension (P_wO_2) although there may be a significant discrepancy between them.[9]

Epidural anesthesia and analgesia attenuates the stress response to surgery, promotes systemic vasodilatation, and provides superior analgesia compared with parenteral methods of analgesia.[10,11] Therefore, we tested the hypothesis that epidural anesthesia and analgesia increases wound tissue oxygen tension when compared with conventional intravenous morphine analgesia.

Methods

Patients

After institutional Ethics Committee approval and written informed consent, we enrolled patients (20–80 yr.) having extensive abdominal or pelvic surgery involving a midline abdominal incision. Patients scheduled for open colon or rectal excision, radical gastrectomy or nephrectomy, total abdominal hysterectomy with bilateral salpin-

* Consultant Senior Lecturer in Anaesthesia, Department of Anaesthesia, Leicester University & University Hospitals of Leicester NHS Trust, Leicester General Hospital, and Mater Misericordiae Hospital, Dublin, Ireland. † Lecturer in Anaesthesia, ‡ Medical Physics Technologist, Department of Anaesthesia, Leicester University & University Hospitals of Leicester NHS Trust, Leicester General Hospital.

Received from the Department of Anaesthesia, Leicester University & University Hospitals of Leicester NHS Trust, Leicester General Hospital, Leicester, UK and Mater Misericordiae Hospital, Dublin, Ireland. Submitted for publication March 12, 2002. Accepted for publication June 11, 2002. This study was funded by a grant from University Hospitals of Leicester, Leicester, UK. Presented in part at the Anaesthetic Research Society, Nottingham UK, November 2001.

Address reprint requests to Dr. Buggy, University Department of Anaesthesia, Mater Hospital, Dublin 7, Ireland. Address electronic mail to donal.buggy@nbsp.ie.

go-oophorectomy, and ovarian cystectomy were included. Patients scheduled for laparoscopic procedures or open laparotomy without a predefined further major procedure were not included. Exclusion criteria were ongoing fever (>37.0°C) or infection, white cell count less than 4,000 or greater than 11,000 cells mm^{-3}, serum albumin less than 30 g/l, use of corticosteroids or immunosuppressant drugs for 4 weeks previously, coagulopathy, (prothrombin time ratio >1.4, activated thromboplastin time >50 s), patients taking vasoactive drugs, and patients for whom either epidural anesthesia or morphine PCA was contraindicated. Ephedrine bolus 3 mg was allowed, at the discretion of the anesthetist, if systemic hypotension occurred.

Randomization

After consenting, each patient was randomly assigned to one of two groups using blocked randomization from a table of random numbers. The assignments were kept in sealed, sequentially numbered envelopes until use. One group of patients received combined general and epidural anesthesia during surgery, followed by patient-controlled epidural analgesia (PCEA) with local anesthetics and fentanyl postoperatively (epidural group); the other group received standard general anesthesia for surgery, followed by intravenous patient-controlled morphine analgesia (PCA) postoperatively (intravenous analgesia group).

Protocol

Patients allocated to the epidural group received a low thoracic (n = 23) or lumbar (n = 9) epidural catheter under local anesthesia, the precise level being at the discretion of the anesthetist caring for the patient. After an initial bolus of 5–10 ml 0.25% plain bupivacaine and 50–100 μg fentanyl, general anesthesia was induced as for the morphine PCA group. Patients received a background continuous epidural infusion of 5–8 ml/h of 0.125% bupivacaine · 4 $\mu g^{-1} \cdot ml^{-1}$ fentanyl during and after surgery. Additional self-administered boluses (2 ml, lock-out time: 30 min) of this mixture were available *via* the epidural route as required by patients in a patient-controlled epidural analgesia (PCEA) facility, which continued for at least 24 h postoperatively. All patients also had an intravenous cannula and fluid giving system attached, but patients were not told whether their patient-controlled analgesia system was epidural or intravenous.

Patients in the morphine PCA group were positioned for epidural anesthesia, but received skin infiltration of local anesthetic only, and had an epidural catheter attached along their back with adhesive tape, as a placebo mock epidural. Intraoperatively, these patients received a loading dose of 0.1 mg/kg morphine and a PCA device prescribed to deliver 1 mg boluses, with a 5-min lockout interval. A 500 ml bag of normal saline with an administration set was attached to their epidural filter, but no infusion was given through it. This was to preserve the patient blinding as far as possible. Anesthetists directly caring for the patients during surgery were, of course, aware of the group allocation, but they took no part in subsequent data collection. Investigators collecting postoperative data were also aware of group allocation, but patients were blind because of giving system attachments both to the epidural filter and intravenous cannula as described. The acute pain (anesthesia) service visited acute postoperative patients at regular intervals to ensure adequacy of continuing analgesia. Patients requiring rescue analgesia received bolus morphine (2 to 3 mg) or bolus epidural analgesia (5–10 ml) as required, according to the mode of analgesia to which they were allocated.

Anesthesia and Fluids

All patients received standard intravenous antibiotic prophylaxis as appropriate 30–60 min prior to the first surgical incision. General anesthesia was induced in all patients with propofol (2.5 mg/kg), fentanyl (1–3 μg/kg) and rocuronium (0.5 mg/kg) and maintained with isoflurane, the dose of which was adjusted to maintain mean arterial pressure (MAP) within 25% of the preinduction values. Close attention was paid to hydration, because hypovolaemia reduces wound perfusion.[12,13] A crystalloid infusion of 10 ml · kg^{-1} · h^{-1} was administered during surgery. The rate of volume infusion was based on the fact that the patients were having major abdominal surgery, and hence could be expected to require 10 ml · kg^{-1} · h^{-1} volume status to meet "third space" losses alone. Further fluid therapy was left to the discretion of the anesthetist, depending on individual patients' requirements.

Blood loss was treated with crystalloid solution using a crystalloid-to-blood ratio of 3:1 or colloid using a colloid-to-blood ratio of 1:1. Packed red cell volume was used as colloid when blood loss exceeded 1,200 ml. All patients had a forced-air warmer (Bair-Hugger 500E, Augustine Medical, La Praye, CH 2608 Courtelary, Switzerland) placed on the upper body before commencement of surgery, and set to 43°C with core temperature monitored by a nasopharyngeal thermistor. In the postoperative period, maintenance crystalloid fluids were given to maintain urine output greater than 0.5 ml · kg^{-1} · h^{-1}. If hypotension (systolic arterial pressure < 90 mmHg) was present, a colloid bolus 5–10 ml/kg was given at the discretion of the attending nurse.

Wound Oxygen Tension and Temperature Monitoring

Wound oxygen tension was measured using a tissue oxygen sensor, located within a subcutaneous, saline-filled tonometer, on a 15 cm probe (CC1-SB, Licox Medical Systems, Integra Neurosciences, Hamps, UK). This was implanted at the end of surgery into the subcutaneous tissue of the wound, along its longitudinal axis with

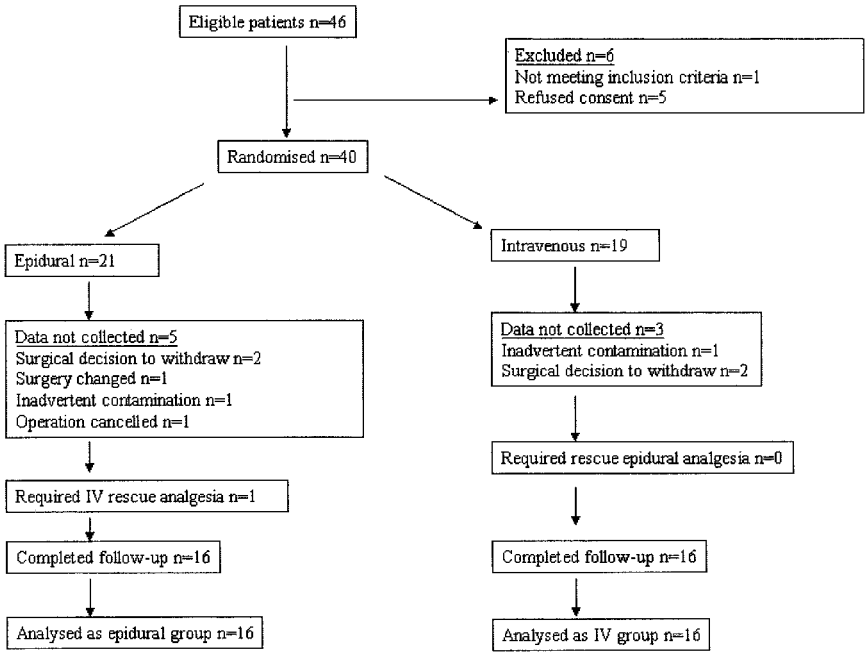

Fig. 1. Study profile.

only the electric connection protruding. The surgeon inserting the probe was unaware of the patient's group assignment. The disposable micro-probe, made of revoxode material, was connected to a digital bedside monitor (Licox CMP, Integra Neurosciences, Hamps, Ltd, UK), which displayed tissue oxygen tension values directly in mmHg, together with a graphical trend. Revoxode probes average the heterogeneous local tissue oxygen tension values over their probe area of 14 mm^2, which eliminates random positioning error of microprobe sensors. Oxygen diffuses from the tissue through the polyethylene wall of the catheter into its inner electrolyte chamber, where the revoxode enables reversible electrolyte reactions to occur at the Clark electrode. This property of the revoxode preserves sensitivity and offset within a narrow range (5%) over a 5 day period of operation.[14] A second probe (CC-10, Integra Neurosciences, Hamps, Ltd, UK) implanted alongside the tissue oxygen sensor enabled local tissue temperature to be measured simultaneously to correct for this variable in P_wO_2 measurements. Both P_wO_2 and wound temperature sensors interface with a laptop PC, allowing data to be recorded on a continuous basis and stored electronically. This technique and equipment is well established for the measurement of P_TO_2.[4,5,8] We created a program from which the averaged hourly values were transferred into an excel spreadsheet for analysis.

Recording of P_wO_2 and wound temperature commenced 30 min after insertion of the last surgical suture. These probes were removed from the patient 24 h later. All patients were kept in the recovery room for at least 1 h, after which they were discharged to the postoperative wards. Postoperatively, all patients received 10 l/min oxygen (FIO_2 = 0.4) *via* a conventional facemask, thus ensuring that tissue oxygen tension remained largely a function of local tissue perfusion.[5,8] This was continued after transfer of patients to the surgical postoperative wards. Patients' arterial oxygen saturation (SaO_2) was monitored continuously postoperatively using standard finger pulse oximetry and stored for subsequent analysis (Propaq 104, Protocol Systems Ltd., Beaverton, Oregon).

Outcome Measures

Primary outcome measures were postoperative P_wO_2, direct wound temperature values and visual analogue pain scores (VAS) at rest and on moving. Pain was recorded at 1, 4, 12, and 24 h postoperatively. Secondary outcome measures included demographic data, physical status of the patients, duration of surgery, total volume of intraoperative and postoperative fluid given, total amount of bupivacaine or morphine given, intraoperative mean arterial pressure, FIO_2, SaO_2 and core temperature, and postoperative MAP and SaO_2. Preoperative full blood count, smoking history, duration of anesthesia and American Society of Anesthesiologists (ASA) risk grade were also recorded. On removal of the wound sensors at the end of the study, each patient was asked to guess their group allocation.

Statistical Analysis

The number of patients required for this trial was estimated as follows: previous studies have shown that additional analgesia can increase P_TO_2 by approximately 25 mmHg, which is clinically significant because this could have a significant impact on surgical wound-infection.[4] The SD of P_TO_2 values in postoperative patients on opioid PCA ranges from 15–33 mmHg, with an average of 25 mmHg.[8] Therefore, accepting a type I error risk of

Table 1. Patient Characteristics

Variable	Epidural Group (n = 16)	Intravenous Analgesia Group (n = 16)	*P* Value (2-tailed)
Age (yr)	59.8 (15.3)	57.8 (16.4)	0.73
Body mass index	25.2 (3.9)	26.8 (3.5)	0.12
Male [n (%)]	12 (75)	12 (75)	1.00
Smoker [n (%)]	3 (19)	3 (19)	1.00
ASA grade I, II, III (n)	4, 8, 4	2, 13, 1	0.70
Preoperative hemoglobin (g/dl)	13.2 (1.9)	13.0 (1.9)	0.90
Type of surgery [n (%)]			
General	7 (44)	6 (37)	0.8
Colorectal	4 (25)	6 (37)	0.6
Urology	3 (19)	0	0.4
Gynecology	2 (12)	4 (25)	0.4

All data are shown as mean (SD) or n (%).

ASA = American Society of Anesthesiologists.

Table 2. Intraoperative Data

Variable	Epidural Group (n = 16)	Intravenous Analgesia Group (n = 16)	*P* Value (2-tailed)
Duration of surgery (hr)	2.9 (1.0)	2.8 (1.3)	0.77
Mean arterial pressure (mmHg)	73.4 (11.7)	89.1 (11.7)	0.001
Ephedrine dose per patient (mg)	6.1 (1.6)	3.3 (1.0)	0.01
Inspired O_2 concentration	0.4 (0.01)	0.4 (0.01)	0.59
Arterial O_2 saturation (%)	98.4 (1.5)	98.3 (1.6)	0.84
End-tidal CO_2 (kPa)	4.4 (0.6)	4.5 (0.4)	0.76
Core temperature (°C)	35.7 (0.4)	36.3 (0.6)	0.004
Crystalloid (l)	2.6 (1.1)	2.5 (1.2)	0.77
Colloid (l)	0.9 (0.3)	0.7 (0.5)	0.19
Blood loss (ml)	710 (520)	588 (353)	0.32

All data are shown as mean (SD).

5% and a type II error risk of 20% (power 80%), 16 patients would be required in each group to evaluate our hypothesis. We used intention-to-treat analysis, *i.e.*, patients were considered to be in the group to which they were assigned (even if epidural failure occurred requiring rescue intravenous analgesia). Hence the denominator for each group was all patients assigned to that group.

Data were analyzed using SPSS v10.0.2 for Windows (SPSS Inc., Chicago, IL) Area under the wound oxygen tension-time curve was calculated using GraphPad Prism v3.0.2 for Windows (Graph Pad Software Inc. San Diego, CA) Repeated measures of intraoperative and postoperative values were averaged over time for each patient and the resulting values averaged among the patients in each group. Comparisons between the study groups were evaluated using unpaired *t* tests, repeat measures for nonparametric data, or chi square tests as appropriate. All *P* values were 2-sided.

Results

Forty-six eligible patients were approached for inclusion in this study. However, six were not randomized because of failure to satisfy the inclusion–exclusion criteria or refused consent. Of 40 patients randomized and consented, data were not collected in eight patients, due to a surgical decision to withdraw patients deemed unsuitable to have oxygen sensors inserted in the wound (n = 4), inadvertent contamination of the sensors in terms of aseptic technique (n = 2) and an unanticipated change in type of surgery (n = 1) or cancellation of surgery (n = 1). The study profile is outlined in figure 1. Oxygen and temperature sensors were placed in all of the remaining 32 patients (n = 16 each group). One patient in the epidural group had failure of analgesia, requiring him to be switched to intravenous patient-controlled analgesia. The patient groups were similar in terms of patient characteristics, prevalence of smoking, ASA grade of physical status and type of surgery (table 1).

Intraoperative and postoperative data are shown in table 2 and table 3, respectively. Values were first averaged across the duration of anesthesia in each patient; the resulting values were then averaged among the patients in each treatment group. Mean arterial pressure was significantly lower in the epidural group both during the intraoperative and postoperative periods. Core temperature was significantly lower during surgery, despite active warming, of patients receiving combined general and epidural anesthesia, as has previously been reported.[15] Cumulative crystalloid and colloid administration was not significantly different between the groups, and adequate postoperative tissue perfusion is suggested by the acceptable hourly urine output observed in both groups. Upper and lower dermatomal sensory levels were recorded in the epidural group (table 3).

Total mean analgesic consumption in epidural (PCEA) patients was 229 ± 64 mg (mean ± SD) of bupivacaine and 326 ± 102 μ) of fentanyl. Total mean morphine consumption was 74 ± 39 mg in intravenous PCA analgesia patients. Both totals account for initial doses and any further rescue boluses given by the acute pain service on the wards. The incidence and approximate timing of need for rescue analgesia is also shown in table 3. Patients receiving intravenous analgesia tended to need more rescue in the first postoperative hour, whereas epidural patients tended to require supplementation between 4–12 h, but there were no significant differences at any time point. The sole epidural patient who required intravenous PCA analgesia received it 6 h postoperatively, however this patient's data were treated as being in the epidural group, consistent with intention-to-treat analysis. Ten patients (63%) in the epidural group compared with eight (50%) in the intravenous group correctly guessed their group allocation when asked directly at the end of the study.

Table 3. Postoperative Data

Variable	Epidural Group (n = 16)	Intravenous Analgesia Group (n = 16)	*P* Value (2-tailed)
Mean arterial pressure (mmHg)	82.3 (10)	98.4 (10.9)	0.015
Arterial O_2 saturation (%)	98 (95–100)	97 (94–100)	0.19
Core temperature (°C)	37.0 (0.5)	37.0 (0.3)	0.50
Crystalloid (l)	2.8 (0.5)	2.9 (0.6)	0.90
Colloid (ml)	0.1 (0.1)	0	0.90
Block level [median (upper, lower)]			
1 hr	T10 (T5, L4)	—	—
4 hr	T10 (T5, L2)	—	—
12 hr	T9 (T6, T11)	—	—
24 hr	T9 (T6, T11)	—	—
Urine output hourly (ml)	66 (20)	72 (32)	0.19
Cumulative no. of patients needing rescue analgesia up to this time			
1 hr	5 (31)	9 (64)	0.18
4 hr	6 (38)	9 (64)	0.80
12 hr	10 (62)	10 (62)	1.00
24 hr	11 (69)	11 (69)	1.00
Mean wound tissue temperature (°C)	38.6 (1.1)	38.4 (0.9)	0.7

Values are mean (SD) or median (range) of all observations taken over the first 24 postoperative hours.

P_wO_2 decreased rapidly in the first 3 h in all patients, then continued to decrease at a slower rate, almost in linear fashion for most of the remainder of the 24 h period (fig. 2). Mean P_wO_2 was significantly higher in the epidural group over the 24 h study period (64.4 ± 14 *vs.* 50.7 ± 15) mmHg, 95% CI difference −22 to −5, $P = 0.002$). Area under the P_wO_2 −24 h time curve was also significantly higher in the epidural group (930 ± 278 *vs.* 749 ± 257) mmHg × h, 95% CI difference −344 to −18, $P = 0.03$) and at several of the hourly epochs (fig. 2).

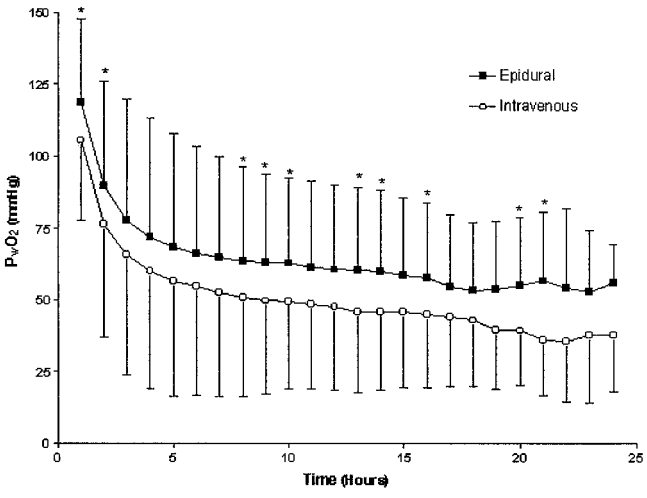

Fig. 2. Wound tissue oxygen tension (P_wO_2) over 24 h. Data are mean (SD). Mean P_wO_2 over the 24 h observation period was significantly higher in the epidural group compared with the intravenous analgesia group (64.4 (14) *versus* 50.7 (15) mmHg, mean (SD), 95% CI difference, −22 to −5, $P = 0.002$). Area under the P_wO_2 −24 h time curve was also significantly higher in the epidural group (930 [278] *versus* 749 ([257] mmHg × h, 95% CI difference −344 to −18, $P = 0.03$). Values are significantly higher in the epidural group compared with the intravenous analgesia group at hours 1, 2, 8, 9, 10, 13, 14, 16, 19 and 20, *$P < 0.05$.

Visual analogue scale (VAS) scores at rest and moving are shown in figure 3. As expected, epidural patients had lower pain scores at all time intervals, both at rest and on

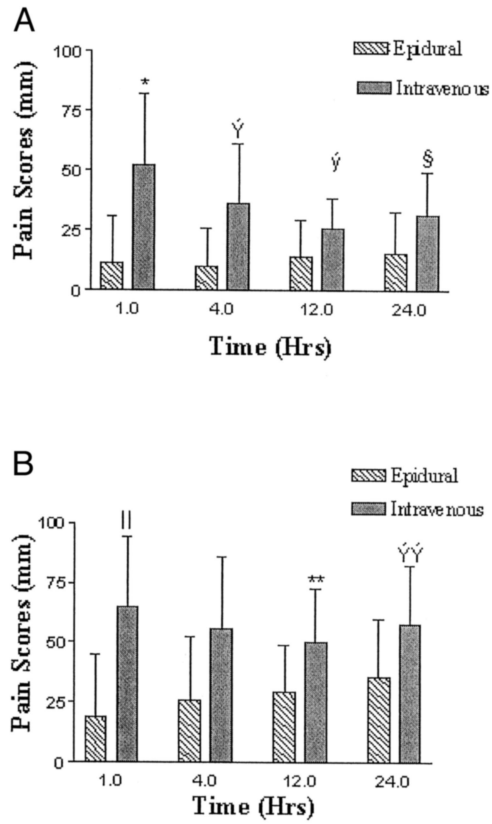

Fig. 3. Visual analogue scores for pain at rest (*A*) and on moving (*B*) over time. Data are median (interquartile range). Scores are significantly lower in the epidural group compared with the intravenous analgesia group both at rest and on moving at all time periods. *$P < 0.001$, †$P = 0.001$, ‡$P = 0.02$, §$P = 0.017$, $P < 0.001$, ¶$P = 0.005$, **$P = 0.011$, ††$P = 0.013$.

moving. Mean postoperative wound tissue temperature showed the same pattern in both groups of an initial low temperature of about 35°C, gradually rising over the next 5 h to reach a plateau of approximately 38.5–39°C for the remainder of the 24-h period. There was no significant difference between the two groups in mean wound temperature over the 24-h period.

Discussion

Conducting major surgery under combined general and epidural anesthesia with epidural postoperative analgesia increased mean wound tissue oxygen tension (P_WO_2) over the first 24 postoperative hours, compared with general anesthesia alone followed by intravenous morphine analgesia. We chose this duration for the study because 24 h is the usual minimum duration of continuing epidural postoperative analgesia, and we wished to evaluate whether any difference in these values would be maintained over a 24 h period. Whether increasing P_WO_2 over a 24-h period influences surgical wound infection and healing is unknown, but increasing it in the intraoperative and first 2 h postoperative is decisive in establishment of surgical-wound infection, although clinically evident infection may not be apparent for several days.[16]

The actual mean difference in P_WO_2 observed (approximately 14 mmHg) is clinically significant, because it has been shown that increasing to this extent could be expected to significantly decrease the risk of surgical-wound infection.[4] This difference in P_WO_2 was apparent despite the fact that our epidural patients were more hypothermic at the end of surgery than those receiving general anesthesia and intravenous analgesia. Patients receiving combined general-epidural anesthesia are more at risk of inadvertent perioperative hypothermia because the epidural prevents thermoregulatory peripheral vasoconstriction from reducing further heat loss during prolonged anesthesia. Epidural anesthesia also further reduces the vasoconstriction threshold compared with general anesthesia alone.[15,17] However, previous work by the Outcomes Research Group has demonstrated that inadvertent, mild, intraoperative hypothermia (core temperature in the region of 34.5–36.0°C) reduces surgical wound healing compared to patients who are maintained normothermic during anesthesia.[18] This confounding effect occurred despite efforts to actively warm all our patients, but its effect would have been to reduce, not increase, P_WO_2 in the epidural group.

The difference in pain scores between epidural and intravenous morphine patients is consistent with other studies comparing these forms of analgesia.[19] Therefore, the greater P_WO_2 in epidural patients may reflect its greater potential for near-total analgesia. This is consistent with the observation of Akça *et al.*, that higher subcutaneous tissue oxygen values were associated with superior analgesia.[8] In the recovery room, breakthrough pain was treated promptly by bolus dosing from the nurse or anesthetist. When patients returned to the wards, the likelihood of prompt remedial action in the event of breakthrough pain was less, although our patients received regular attention from the acute pain service. Epidural failure may occur as often as 25–30%[20,21] although only one patient in our epidural group required rescue intravenous morphine analgesia. Dermatomal sensory level in epidural patients remained at an adequate level throughout the 24-h period, except in the one patient who required rescue intravenous patient controlled analgesia. This patient was classified as having had epidural analgesia for the 24-h period, because we used intention-to-treat analysis.

It is possible that the difference in P_WO_2 we observed in epidural patients was caused by greater attenuation of the surgical stress response by epidural anesthesia. We did not measure indices of the surgical stress response, but it is well established that preemptive use of epidural anesthesia (*i.e.*, ensuring a functional block before the first surgical incision) attenuates it. Therefore, postoperative sympathetic nervous system activity is reduced, and superior analgesia provided compared with intravenous analgesia. However, an intrinsic vasodilatory property, resulting in improved tissue perfusion, may be an alternative explanation. It is likely that optimum benefit from epidural analgesia follows from its use during both the intraoperative and postoperative period.[7,11,21,22]

We measured wound oxygen tension (P_WO_2) directly, to avoid concerns about discrepancies between measurements taken at a site distal from the site of surgery[9] in contrast to previous studies, which inferred P_WO_2 from subcutaneous tissue oxygen values (P_TO_2) obtained distal from the actual wound site.[5,8] A simultaneous comparison of measurements of P_WO_2 in surgical wounds and subcutaneous tissue indicated that oxygen tension measured directly in the wound was consistently lower than in subcutaneous tissue, presumably resulting from greater disruption of local blood supply and infiltration with inflammatory cells.[9] Another study evaluated the effect of bolus doses of epidural local anesthetic on postoperative patients after major surgery. Intermittent, rather than continuous, measurements of P_TO_2 were unchanged after the epidural bolus, irrespective of the inspired oxygen concentration. However, this study was conducted on day 2 postoperatively, when the relationship between tissue perfusion, P_WO_2 and postoperative pain may have altered from the first 24 h. Moreover, pain and was not evaluated, transcutaneous oxygen sensors were used subcutaneously, and were placed 5 to 6 cm lateral to the surgical wound rather than directly in it.[23]

Postoperative P_WO_2 was characterized by an initial rapid decrease over the first 3 to 4 h, followed by a more gradual linear decrease over the remaining 18–24 h. Our initially high values may represent incomplete equilibra-

tion caused by air trapping in the wound when it was closed. The probe is designed for measurement of parenchymal tissue oxygen tension. It is a revoxode probe, which averages the local tissue oxygen tension values over its oxygen sensitive area of 14 mm^2. In addition, its electrochemical reactions are reversible, thereby preserving sensitivity, offset and drift over a 5 day period.[24] Our observation is consistent with that of others, who reported gradual decreases in intermittent, once-daily, measurements on successive postoperative days.[9,25] Initially, P_WO_2 is high because of fresh bleeding into the wound, but decreases rapidly as vessels thrombose and inflammatory cells, which consume oxygen, accumulate.[26] Major surgery is associated with a greater depression of P_WO_2, which may reflect greater sympathetic nervous system activation after major compared with minor surgery.[9,25]

Although about half of our patients became aware of their group allocation in this study, there was no significant difference between the groups, suggesting random chance.

More importantly, the primary outcomes were objective measurements. Many confounding variables may affect P_WO_2, including tissue perfusion and hemoglobin concentration,[12] smoking prevalence,[26,27] intraoperative inadvertent hypothermia,[18] and oxygen therapy.[5] With the exception of intraoperative hypothermia, discussed previously, all these factors were similar between the groups. Oxygen therapy was administered to all patients postoperatively, to minimize the impact of inadequate postoperative ventilation, thus making tissue oxygen tension predominantly dependent on local perfusion.[12]

Continuous arterial saturation monitoring postoperatively demonstrated similar high values between the groups, suggesting good compliance with oxygen therapy. Intraoperative mean arterial pressure was lower in epidural patients, which is consistent with the hemodynamic effect expected of a functional epidural, but was entirely within a clinically acceptable range. Fluid administration intra- and postoperatively was also comparable between the groups, suggesting that tissue perfusion was well maintained. The patients studied had similar preoperative hemoglobin and intraoperative blood loss, although recent work has shown that P_TO_2 is maintained in healthy volunteers despite isovolemic anemia to a hemoglobin concentration of 5 g/dL, suggesting that severe anemia may not be a major determinant of P_WO_2.[13]

In conclusion, this prospective, randomized, single-blind clinical trial has shown that patients receiving epidural anesthesia and postoperative analgesia with general anesthesia for major surgery have higher postoperative wound oxygen tension than patients receiving general anesthesia and intravenous morphine analgesia. Subcutaneous wound tissue oxygen tension is a major determinant of surgical wound infection and healing. A large-scale, multicenter, randomized, controlled trial is warranted, similar to others of the Outcomes Research Group,[5,11] comparing epidural and intravenous analgesia with wound infection as the primary outcome.

We thank our anesthesia, surgical, and nursing colleagues for their support and cooperation, and our patients for participating in this work.

References

1. Bremmelgaard A, Raahave D, Beier-Holgersen R, Pedersen JV, Andersen S, Sorensen AI: Computer-aided surveillance of surgical infections and identification of risk factors. J Hosp Infect 1989; 13:1–18
2. Allen DB, Maguire JJ, Mahdavian M, Wicke C, Marcocci L, Scheuenstuhl H, Chang M, Le AX, Hopf HW, Hunt TK: Wound hypoxia and acidosis limit neutrophil bacterial killing mechanisms. Arch Surg 1997; 132:991–6
3. Prockop DJ, Kivirikko KI, Tuderman L, Guzman NA: The biosynthesis of collagen and its disorders. N Engl J Med 1979; 301:13–23
4. Hopf HW, Hunt TK, West JM: Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg 1997; 132:997–1005
5. Greif R, Akca O, Horne P, Curz A, Sessler DI: Supplemental perioperative oxygen to reduce the incidence of surgical wound infection. N Engl J Med 2000; 342:161–7
6. Buggy DJ: Can anaesthetic management influence surgical wound healing? Lancet 2000; 356:355–7
7. Kehlet H, Holte K: Effect of post-operative analgesia on surgical outcome. Br J Anaesth 2001; 87:62–72
8. Akça O, Melischek M, Scheck T, Hellwagner K, Arkilic CF, Kurz A, Kapral S, Heinz T, Lackner FX, Sessler DI: Postoperative pain and subcutaneous oxygen tension. Lancet 1999; 354:41–2
9. Chang N, Goodson WH, Gottrup F, Hunt TK: Direct measurement of wound and tissue oxygen tension in postoperative patients. Ann Surg 1983; 197:470–8
10. Buggy DJ, Smith G: Epidural anesthesia and analgesia: better outcome after major surgery? BMJ 1999; 319:530–1
11. Liu S, Carpenter RL, Neal JM: Epidural anesthesia and analgesia: Their role in postoperative outcome. ANESTHESIOLOGY 1995; 82:1474–506
12. Jonsson K, Jensen JA, Goodson WH, West JM, Hunt TK: Assessment of perfusion in postoperative patients using tissue oxygen measurements. Br J Surg 1987; 74:263–7
13. Hopf HW, Viele M, Watson JJ, Feiner J, Weiskopf R, Hunt TK, Noorani M, Yeap H, Ho R, Toy P: Subcutaneous perfusion and oxygen during acute severe isovolemic hemodilution in healthy volunteers. Arch Surg 2000; 135:1443–9
14. Dings J, Meixensberger J, Jager A, Roosen K Clinical experience with 118 brain tissue oxygen partial pressure catheter probes. Neurosurgery 1998; 43: 1082–95
15. Joris J, Ozaki M, Sessler DI, Hardy AF, Lamy M, McGuire J, Blanchard D, Schroeder M, Moayeri A: Epidural anesthesia impairs both central and peripheral thermoregulatory control during general anesthesia. ANESTHESIOLOGY 1994; 80:268–77
16. Miles AA, Miles EM, Burke J: The value and duration of defense reactions of the skin to the primary lodgement of bacteria. Br J Exp Pathol 1957; 38:79–96
17. Buggy DJ, Crossley AWA: Thermoregulation, mild perioperative hypothermia and post-anaesthetic shivering. Br J Anaesth 2000; 84:615–28
18. Kurz A, Sessler DI, Lenhardt R: Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalisation. N Engl J Med 1996; 334:1209–15
19. Mann C, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G, Domergue J, Millat B, Colson P: Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery ANESTHESIOLOGY 2000; 92(2):433–41
20. McLeod G, Davies H, Munnoch N, Bannister J, MacRae W: Postoperative pain relief using thoracic epidural analgesia: Outstanding success and disappointing failures. Anesthesia 2001; 56:75–81
21. Wheatley RG, Schug SA, Watson D: Safety and efficacy of postoperative epidural analgesia. Br J Anaesth 2001; 87:47–61
22. Kehlet H: Modification of responses to surgery by neural blockade: Clinical implications, Neural Blockade in Clinical Anesthesia and Management of Pain, 3rd edition. Edited by Cousins MJ, Bridenbaugh D. Philadelphia, Lippincott-Raven, 1998; pp 129–71
23. Rosenberg J, Pedersen U, Erichsen CJ, Vibits H, Moesgaard F, Kehlet H: Effect of epidural blockade and oxygen therapy on changes in subcutaneous oxygen tension after abdominal surgery. J Surg Res 1994; 56:72–6
24. van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ, Suazo JA, Hogesteeger C, Jansen WJ, Kloos LM, Vermeulen J, Maas AI: Brain oxygen tension in severe head injury. Neurosurgery 2000; 46(4):868–76
25. Gottrup F, Firmin R, Rabkin J, Halliday BJ, Hunt TK: Directly measured tissue oxygen tension and arterial oxygen tension assess tissue perfusion. Crit Care Med 1987; 15:1030–6
26. Nortcliffe SA, Buggy DJ: Implications for anesthesia of infection and wound healing. Intl Anesthesiol Clin N Am 2003 [in press]
27. Jensen JA, Goodson WH, Hopf HW, Hunt TK: Cigarette smoking decreases tissue oxygen. Arch Surg 1991; 126:1131–4