EFFECTS OF EXTRADURAL BUPIVACAINE ON THE HAEMOSTATIC SYSTEM


The incidence of thromboembolic complications after total hip replacement is lower in patients operated on under extradural analgesia than in similar patients receiving general anaesthesia (Modig et al., 1981; Modig et al., 1983a; Modig et al., 1983b). It is claimed that this phenomenon is the result of a combination of rheological changes (Modig, Malmberg and Karlström, 1980) and an increase in activity in the fibrinolytic system (Simpson et al., 1982; Modig et al., 1983a; Modig et al. 1983b). In addition, there is a significant decrease in intraoperative blood loss in patients under extradural analgesia compared with those receiving general anaesthesia (Moir, 1968; Bond, 1969; Zorgnotti, Naris and Dell'Aria, 1970; Stanton-Hicks, 1971; Fasth et al., 1972; Thorud, Lund and Holme, 1975; Keith, 1977; Modig et al., 1981; Modig et al., 1983a; Modig et al., 1983b). Although earlier reports have demonstrated the inhibitory effects of local analgesic drugs on platelet aggregation (Aledort and Niemetz, 1968; Feinstein, Fiekers and Fraser, 1976), to our knowledge, there are no reports on the effects of bupivacaine on platelet function. Thus we have studied the influence of general anaesthesia, and extradural analgesia with bupivacaine, on platelet function and on the fibrinolytic and coagulation systems.

SUMMARY

Twenty consecutive patients undergoing elective transurethral resection of the prostate were allocated randomly to one of two groups. Group I (n = 10) received lumbar extradural analgesia with 0.5% bupivacaine. Group II (n = 10) received general anaesthesia with spontaneous respiration, using 60% nitrous oxide and 1–2% halothane in oxygen. There was a significant inhibitory effect on platelet aggregation in the extradural group. No such effect was observed in the general anaesthesia group. Measured indices of coagulation and fibrinolysis showed no abnormalities compared with control in either group except for a significant decrease in alpha2-antiplasmin during surgery in group II. These results suggest that the possible thrombo- prophylactic effect of extradural analgesia with bupivacaine may result from an inhibitory effect on platelet aggregation which is in addition to the increase in lower limb blood flow.

PATIENTS AND METHODS

Twenty consecutive patients undergoing elective transurethral resection of the prostate were allocated randomly to one of two groups. Group I (n = 10) received lumbar extradural analgesia with 0.5% bupivacaine and group II (n = 10) received general anaesthesia. Informed consent was obtained from each patient. Exclusion criteria were coagulation, haemostatic or fibrinolytic abnormalities or the use of drugs known to influence platelet function. All patients received subcutaneous sodium heparin 5000 iu twice daily. This was started before surgery and continued for 3 days until the patients were mobilized.
All patients received, as premedication, nico-
morphine 7.5 mg and atropine 0.5 mg i.m., and
lorazepam 1 mg by mouth 45 min before surgery.
Dextrose 5% in lactated Ringer's solution was
given at a rate of 10 ml kg\(^{-1}\) h\(^{-1}\) during the
operation. Blood loss was replaced with concen-
trated red cells.

**Extradural analgesia**

Extradural blockade was achieved with 0.5%
plain bupivacaine 15 ml. Vasopressor drugs were
not used to correct any hypotension during
surgery. After surgery, these patients were given
0.5% bupivacaine 4–5 ml as required and no
parenteral analgesics were administered. Although
these patients were receiving prophylactic anti-
coagulation, it has been shown that the occurrence
of symptomatic haematoma following the place-
ment of extradural or subarachnoid catheters is a
rare complication (Rao and El-Etr, 1981; Odoom
and Sih, 1983).

**General anaesthesia**

Anaesthesia was induced with methohexitone
0.75 mg kg\(^{-1}\) and suxamethonium 1 mg kg\(^{-1}\) was
given to facilitate intubation of the trachea.
Anaesthesia was maintained with 60% nitrous
oxide and 1–2% halothane in oxygen. Patients
were allowed to breathe spontaneously via a
semi-closed circle system with a gas flow of 6
litre min\(^{-1}\). After surgery, nicomorphine 7.5 mg
was given i.m. for pain relief, as required.

**Blood sampling**

Venous blood samples were taken on the day
before surgery, 15 min before the induction of
anaesthesia, every 30 min during surgery, 10 min
after the end of surgery and then daily for the
following 3 days.

**Investigations**

Venous blood, 9 volumes was collected into
plastic tubes containing 1 volume of 3.2%
trisodium citrate dihydrate for platelet aggregation
and release studies. Platelet-rich plasma (PRP)
was obtained by centrifugation at 160 g for 10 min
at room temperature. Platelet-poor plasma (PPP)
was obtained by further centrifugation at 2700 g
for 10 min and used for aggregometer adjustment
at 100% transmission. Platelet aggregation studies
were performed at 37 °C using a Payton Dual
Channel aggregometer (Payton Ltd, Scarborough,
Ontario, Canada). PRP samples, 0.38 ml, stirred
at 900 rev min\(^{-1}\) were challenged with adenosine
diphosphate (ADP) 0.02 ml (Sigma Chemical Co.,
Saint Louis, Missouri, U.S.A.) and with collagen
0.02 ml (General Diagnostics, Morris Plains,
New Jersey, U.S.A.) at final concentrations of
0.6–1.0 µmol litre\(^{-1}\) and 0.4 µg ml\(^{-1}\), respectively.
Concurrent aggregation and adenosine triphos-
phate (ATP) release studies were performed at
37 °C using a Chrono-Log Lumi Aggregometer,
model 400 (Chrono-Log Corp., Havertown, PA,
U.S.A.).

Coagulation and fibrinolytic studies were per-
fomed using plasma obtained from blood col-
lected into plastic tubes containing solid K\(_2\)-
EDTA (1.5 mg per ml blood). EDTA-plasma was
used for the automated chromogenic determina-
tion of antithrombin III (ATIII) (Kahle et al.,
1978), alpha-antiplasmin (α\(_t\)-AP), plasminogen,
factor II (Peters et al., 1982) and factor X (van
Wijk, Kahle and ten Cate, 1980). Plasma samples
were prepared by centrifugation at 1700 g for
10 min at room temperature and rendered platele-
poor by a second run at 12000 g for 4 min
in a table centrifuge. Reference pooled plasma
was obtained from 40 healthy volunteers (sex
ratio 1:1). Small aliquots were stored in plastic
tubes at −70 °C.

**Statistical methods**

The results are expressed as mean values
± SEM. Significance was assessed using a paired
Student's \(t\) test. A value of \(P < 0.05\) was
considered significant.

**RESULTS**

Details of the patients studied are shown in table
I. The two groups did not differ with respect to
age, weight and duration of surgery.

Representative platelet aggregation curves from

| Table I. Patient details (mean ± SEM). Significantly different from general anaesthesia group: * \(P < 0.01\) |
|-----------------|-----------------|-----------------|
| Age (yr)        | 61.6 ± 1.4      | 61.1 ± 2.4      |
| Duration of surgery (min) | 70.5 ± 10.7 | 68.0 ± 8.2 |
| Intraoperative blood transfusion (ml) | 600.0 ± 77.5 | 490 ± 52.6* |
| Immediate postoperative haematocrit (%) | 39.5 ± 1.3 | 39.2 ± 0.9 |
one patient are illustrated in figures 1 and 2. Aggregation was measured by two indices: speed and height. Speed of aggregation is expressed as the tangent of the steepest part of the slope of the aggregation curve; height is expressed in mm from the baseline. The changes in platelet aggregation and in measured coagulation and fibrinolytic variables are shown in table II. There was a significant decrease \((P < 0.001)\) in aggregation height in the extradural group. No change in platelet function occurred in the general anaesthetic group. There was a small, but statistically significant \((P < 0.05)\), decrease in \(\alpha_2\)AP in the general anaesthetic group, although the values...
during anaesthesia remained within the range accepted as normal. There were no changes in plasminogen, antithrombin III, factor II or factor X in either group.

For technical reasons it was not possible to measure accurately total blood loss in our patients. However, concentrated red cells were given to replace the estimated blood loss. The haematocrit immediately after surgery was normal in both groups (table I). Significantly more blood \((P < 0.01)\) was given to patients receiving general anaesthesia \((600 \pm 24.5 \text{ ml})\) than to those in the extradural group \((490 \pm 52.6 \text{ ml})\).

**DISCUSSION**

The results of this study demonstrate that extradural analgesia using 0.5% bupivacaine has an inhibitory effect on platelet aggregation and release. No effect of general anaesthesia was observed on measured platelet function, a finding similar to that reported by Lichtenfeld, Schiffer and Helrich (1979). It is unlikely that either the premedication or the surgical procedure induced the observed effects, since these were similar in both groups. Primary haemostasis (in other words platelet aggregation activity) plays an important role in the initiation of thrombus formation. Our findings of an inhibition of platelet aggregation may explain one facet of the thrombo-prophylactic effect of extradural analgesia with bupivacaine as described by Modig and colleagues (Modig et al., 1981; Modig et al., 1983b).

Although a statistically significant decrease in \(\alpha_1\)-AP was found in the general anaesthetic group, all values were within the normal range \((0.81-1.40 \text{ u ml}^{-1})\). The decrease in \(\alpha_1\)-AP in the general anaesthetic group suggests an increase in fibrinolytic activity. This finding is consistent with the results of Simpson and colleagues (1982), who found a significant enhancement of fibrinolytic activity during extradural analgesia with bupivacaine as described by Modig and colleagues (Modig et al., 1981; Modig et al., 1983b).

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Our observations are in contrast to the findings of Modig and colleagues (1983a), who found lower fibrinolytic inhibitory activity, a higher resting concentration of plasminogen activators and increased capacity of venous endothelium to release plasminogen activators in patients receiving extradural analgesia, as compared with general anaesthesia—findings which are compatible with an increase in fibrinolytic activity. However, these workers used a local analgesic solution containing adrenaline 5 \(\mu\text{g ml}^{-1}\), which is known to enhance plasminogen activator release. Furthermore, the authors noted a decrease in fibrinolysis inhibition for up to 6 days and increased resting concentration of plasminogen activators for up to 2 days after the administration of the bupivacaine had been discontinued.

Although venous stasis, stress, malignancies, catecholamine-like substances, vasodilators and several other factors can influence fibrinolysis (Kernoff and McNicol, 1977; Emeis, 1979), it is likely that no single factor activates the fibrinolytic system. However, the administration of ephedrine 50 mg before extradural blockade and the use of local analgesic solutions containing adrenaline 5 \(\mu\text{g ml}^{-1}\) for the first 24 h could be held partly responsible for the findings of Modig and colleagues (1983a). I.v. administration of bupivacaine to achieve a plasma concentration of 1-2 \(\mu\text{g ml}^{-1}\) (comparable to those achieved by extradural analgesia (Moore et al., 1979)) significantly increased adrenaline concentration from 0.03 to 0.08 ng ml\(^{-1}\) (Hasselstrem et al., 1984).

The effect of this increase on the haemostatic system requires evaluation.

Although blood loss was not measured in this study, it was interesting to note a significant increase in the volume of blood transfused in the patients receiving general anaesthesia. This is in agreement with the findings of Modig and co-workers (1983b).

In conclusion, we have demonstrated a significant inhibition of platelet aggregation without any increased effect on fibrinolysis. The inhibition of platelet function may play a role in reducing the incidence of venous thromboembolic complications in patients receiving extradural analgesia.

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