CARDIOVASCULAR AND BIOCHEMICAL EVIDENCE OF STRESS DURING MAJOR SURGERY ASSOCIATED WITH DIFFERENT TECHNIQUES OF ANAESTHESIA

W. P. BLUNNIE, P. D. A. MCIILROY, J. D. MERRETT AND J. W. DUNDEE

SUMMARY

The relative merits of a potent narcotic and a spinal analgesic to affect the stress response to a standard operation have been assessed. Forty-five fit patients scheduled for abdominal hysterectomy were allocated at random to three groups, referred to as standard (i.v. anaesthesia alone), spinal (spinal plus i.v. anaesthesia) and fentanyl (fentanyl plus i.v. anaesthesia) groups. In the doses used, fentanyl produced the most effective attenuation of the cardiovascular, hormonal and metabolic responses to stress, but had the disadvantage of prolonged respiratory depression. Spinal anaesthesia gave only a modified blockade of the response to stress and did not obviate the response to intubation.

Since most of the commonly used i.v. induction agents do not possess analgesic properties their use in total i.v. anaesthesia may result in problems from the unsuppressed response to stress (Clarke, 1970; Hall et al., 1978; Wood, 1978). Attempts to measure the stress response to surgery show that cardiovascular, biochemical and hormonal changes are involved (Savege, 1978).

Analgesia during operation can be provided by potent narcotics or, in appropriate circumstances, by spinal or extradural analgesia. The relative merits of these have not been assessed as regards their ability to obtund the stress response to a standard operation. This paper reports a comparison of the effects of total i.v. anaesthesia alone, with this technique supplemented by either high-dose fentanyl or spinal anaesthesia in three groups of patients undergoing abdominal hysterectomy. A preliminary report has been published by Blunnie and colleagues (1982).

PATIENTS AND METHODS

Forty-five fit patients (ASA I and II) scheduled for abdominal hysterectomy, were allocated at random to three treatment groups referred to as standard (i.v. anaesthesia alone), spinal (spinal plus i.v. anaesthesia) and fentanyl (fentanyl plus i.v. anaesthesia) groups. All conformed to preset criteria for age, weight and height so that three comparable groups were obtained (table I). The study was approved by the regional Ethics Committee and verbal consent was obtained from each patient.

A standard premedication of lorazepam 4 mg was given by mouth 2 h before surgery. In the anaesthetic room the effect of the premedication was assessed (Dundee, Moore and Nicholl, 1962) and resting arterial pressure and heart rate were recorded. Cannulae (16 s.w.g.) were inserted into each arm under local anaesthesia, for the administration of drugs and for the repeated sampling of venous blood. The standard anaesthetic technique consisted of induction with Althesin followed by the administration of pancuronium 100 μg kg⁻¹ to provide neuromuscular blockade and facilitate the passage of an 8-mm cuffed oral endotracheal tube. Anaesthesia was maintained with an infusion of 10% Althesin in compound sodium lactate solution B.P. The infusion rate was set at 2 ml min⁻¹ and was adjusted according to the patient’s needs. Analysis of dosage was limited to the first 40 min of anaesthesia (table III). Respiration was maintained by intermittent positive pressure ventilation with P<sub>0.2</sub> 0.5 in nitrogen at a tidal volume of 10 ml kg⁻¹ at a rate of 10 b.p.m. Neuromuscular blockade was reversed...
with a mixture of atropine 1.8 mg (3 ml) and neostigmine 5.0 mg (2 ml) at a dose of 1 ml/20 kg.

Before the induction of anaesthesia one group received a spinal anaesthetic using 1.6–2.0 ml of 0.5% cinchocaine in 6% dextrose. Hypotension was prevented by infusing i.v. a solution of compound sodium lactate B.P. After ensuring that the sensory block was adequate (T10), general anaesthesia was induced as above.

The third group received fentanyl 20 μg kg\(^{-1}\) given over a period of 5 min, after which anaesthesia was induced and continued as above.

Arterial pressure (Riva Rocci method) and heart rate were recorded at 5-min intervals throughout all operations.

Papaveretum, given on demand, was the standard postoperative analgesic and the requirements during the first 24 h were noted.

Blood was drawn for biochemical and hormonal analyses at skin incision (zero time) and at 30, 60, 90, 120 min and 3, 4, 24 and 48 h. The samples were either analysed immediately (plasma glucose and free fatty acids) or separated and stored at −20°C until the analysis could be carried out (plasma cortisol, prolactin and human growth hormone).

Plasma glucose concentration was measured on a Technicon auto-analyser II system using the glucose oxidase method. Radioimmunoassay was used to measure the concentrations of plasma cortisol (Riad et al., 1979), prolactin (Groom, 1977) and human growth hormone (Hunter, 1976). The concentration of free fatty acids was estimated by a colorimetric method (Duncombe, 1964).

After the induction of anaesthesia a Salem sump, double-lumen stomach tube was passed and gastric contents emptied at time zero and at 30, 60, 90, 120 and 180 min for the estimation of volume and pH.

Before skin incision a self-retaining urinary catheter was passed and clamped. This was released on a 4-hourly basis for 24 h and urine passed directly into a bottle containing concentrated hydrochloric acid 10 ml as preservative. Urinary catecholamine concentrations were estimated from this sample and from one collected by the patient in the preceding 24 h.

**RESULTS**

There were no significant differences between the duration of fasting, the time between premedication and anaesthesia or the duration of operation in the three groups. However, the anaesthetic time was significantly prolonged in the fentanyl group because of the respiratory depressant effect of the drug (table II).

Table III shows doses of Althesin administered at induction and for maintenance (for the first 40 min), and also the total dose of Althesin given, expressed as total steroid, in all three series. Dose regimen differed across the series, as this was based on the needs of the patients as judged on a clinical basis, smaller induction and maintenance doses being required in those patients pre-treated with fentanyl.

**Cardiovascular system**

Figures 1 and 2 record the mean systolic arterial pressures and heart rates in the three series. For the sake of clarity the scatter of the readings is not given. In general, the diastolic pressure followed the same pattern as the systolic and is not reported.

The increases in the heart rate and systolic arterial pressure were greatest in those patients who did not have an analgesic. During the period of operation the difference between the response in the standard and the other two groups was significant (P < 0.001). In the doses used, fentanyl abolished the hypertensive response to tracheal intubation; this occurred to a lesser degree in the spinal series.

**TABLE II. Comparability of series (mean time (min) ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Spinal</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fasting</td>
<td>657 ± 26</td>
<td>671 ± 27</td>
<td>659 ± 34</td>
</tr>
<tr>
<td>Premedication to</td>
<td>112 ± 6</td>
<td>108 ± 6</td>
<td>114 ± 7</td>
</tr>
<tr>
<td>anaesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of operation</td>
<td>62 ± 3</td>
<td>65 ± 4</td>
<td>66 ± 6</td>
</tr>
<tr>
<td>Duration of anaesthesia</td>
<td>81 ± 5</td>
<td>85 ± 4</td>
<td>120 ± 4</td>
</tr>
</tbody>
</table>

**TABLE III. Mean induction, maintenance and total doses of Althesin, expressed as mg of steroid**

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Spinal</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>37.4</td>
<td>40.2</td>
<td>27.2</td>
</tr>
<tr>
<td>0–5 min</td>
<td>19.2</td>
<td>12.6</td>
<td>9.7</td>
</tr>
<tr>
<td>5–10 min</td>
<td>19.5</td>
<td>12.1</td>
<td>9.8</td>
</tr>
<tr>
<td>10–15 min</td>
<td>20.2</td>
<td>11.3</td>
<td>9.1</td>
</tr>
<tr>
<td>15–20 min</td>
<td>16.6</td>
<td>13.7</td>
<td>8.8</td>
</tr>
<tr>
<td>20–25 min</td>
<td>16.3</td>
<td>12.7</td>
<td>8.5</td>
</tr>
<tr>
<td>25–30 min</td>
<td>14.9</td>
<td>11.5</td>
<td>8.9</td>
</tr>
<tr>
<td>30–35 min</td>
<td>13.9</td>
<td>11.8</td>
<td>8.7</td>
</tr>
<tr>
<td>35–40 min</td>
<td>13.2</td>
<td>11.8</td>
<td>8.7</td>
</tr>
<tr>
<td>Total for full operating time</td>
<td>238.4</td>
<td>170.5</td>
<td>143.1</td>
</tr>
</tbody>
</table>
STRESS DURING MAJOR SURGERY

Fig. 1. Mean systolic arterial pressure in three series of patients anaesthetized with standard infusion technique alone (□), infusion with spinal analgesia (●) and infusion with a single high dose of fentanyl (▲). 

x = Induction and end of anaesthesia; ↓ = tracheal intubation; ◊ = skin incision; ↑ = tracheal extubation.

Fig. 2. Mean heart rate in three series of patients anaesthetized with standard infusion technique alone (□), infusion with spinal analgesia (●) and infusion with a single high dose of fentanyl (▲). Symbols as for figure 1.

Biochemical indices

Plasma glucose concentration. There was a progressive increase in mean plasma glucose concentration in all three series, reaching a peak with the standard anaesthetic technique at 60 min and in the spinal series at 90 min (fig. 3). Thereafter, it decreased gradually in both series. In those patients given fentanyl the increase was less marked and did not peak until 180 min. The probability values for comparison of concentrations are given in table IV;

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FIG. 3. Mean (±SEM) plasma glucose concentrations (mmol litre\(^{-1}\)) in three series of patients anaesthetized with standard infusion technique alone (\(\bigcirc\)), infusion with spinal analgesia (\(\bullet\)) and infusion with a single high dose of fentanyl (\(\Delta\)). Significance of difference between series, calculated by the Friedman analyses of variance: *\(P<0.05\); **\(P<0.01\); ***\(P<0.001\).

**Table IV. P values for comparison of plasma glucose concentrations at times shown, calculated using the Wilcoxon Matched Pairs Signed Ranks Test**

<table>
<thead>
<tr>
<th>Time of observation</th>
<th>Standard v. spinal</th>
<th>Standard v. fentanyl</th>
<th>Spinal v. fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>0.995</td>
<td>0.460</td>
<td>0.463</td>
</tr>
<tr>
<td>Skin incision</td>
<td>0.712</td>
<td>0.778</td>
<td>0.307</td>
</tr>
<tr>
<td>+ 30 min</td>
<td>0.001</td>
<td>0.003</td>
<td>0.364</td>
</tr>
<tr>
<td>+ 60 min</td>
<td>0.001</td>
<td>0.002</td>
<td>0.212</td>
</tr>
<tr>
<td>+ 90 min</td>
<td>0.009</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>+ 120 min</td>
<td>0.222</td>
<td>0.005</td>
<td>0.006</td>
</tr>
<tr>
<td>+ 180 min</td>
<td>0.087</td>
<td>0.065</td>
<td>0.490</td>
</tr>
<tr>
<td>+ 240 min</td>
<td>0.061</td>
<td>0.047</td>
<td>0.650</td>
</tr>
<tr>
<td>+ 24 h</td>
<td>0.730</td>
<td>0.307</td>
<td>0.553</td>
</tr>
<tr>
<td>+ 48 h</td>
<td>0.683</td>
<td>0.307</td>
<td>0.427</td>
</tr>
</tbody>
</table>

Plasma cortisol concentration. Protection against increases in the plasma cortisol concentration was provided by both the spinal and fentanyl techniques, as compared with standard infusion anaesthesia, for up to 240 min. During this time, fentanyl was more effective than the spinal (fig. 4), this difference reaching statistical significance (\(P<0.001\)).

Plasma prolactin concentration. Plasma prolactin concentration increased to a significant degree (\(P<0.05\)) with all techniques – reaching a peak at 30 min and declining thereafter (fig. 5). In general, the lowest values occurred in the spinal series, but the differences between series were not statistically significant at any time.

Plasma growth hormone concentration. There was a large between-patient variation in plasma growth hormone concentrations which were more markedly increased in the standard series than in the supplementary techniques (fig. 6), the differences being significant (\(P<0.02\)) between 30 and 180 min in the spinal series and at 30 and 120 min in the fentanyl group. Although at no time did the concentration increase in the spinal series the means did not differ significantly from those observed with fentanyl.

These indicate a significantly greater increase in plasma glucose concentration in patients anaesthetized with the standard infusion technique compared with both other series up to 90 min and with the fentanyl series up to 120 min. Thereafter, although the increases were still more marked with the standard technique, under the statistical tests used they did not reach significance compared with either of the other series. The increases noted in the fentanyl series were significantly less than in the spinal series at 90 and 120 min.
STRESS DURING MAJOR SURGERY

Fig. 4. Mean (±SEM) plasma cortisol concentrations (mmol litre⁻¹) in three series of patients anaesthetized with standard infusion technique alone (□), infusion with spinal analgesia (●) and infusion with a single high dose of fentanyl (▲). Significance of difference between series, calculated by the Friedman analyses of variance: *P < 0.05; **P < 0.01; ***P < 0.001.

Plasma free fatty acids. There was a large scatter between individual concentrations of free fatty acids as indicated by the standard errors of the means in figure 7. Differences between mean concentrations with the individual anaesthetic techniques were not significant except at 30 min where the spinal techni-

Fig. 5. Mean (±SEM) plasma prolactin concentration (μU. litre⁻¹) in three series of patients anaesthetized with standard infusion technique alone (□), infusion with spinal analgesia (●) and infusion with a single high dose of fentanyl (▲).
The comprehensive study differed from other reported series in having a standard non-analgesic technique, even to the exclusion of nitrous oxide (George et al., 1974; Brandt et al., 1976; Kehlet et al., 1979).

Table VI concisely summarizes the overall changes in plasma concentrations of the hormones or biochemical variables studied. In the doses used fentanyl produced the more effective attenuation of the stress response as defined and measured in this study. However, in operations of this duration, the moderate doses of fentanyl used did have the disadvantage that prolonged respiratory depression was accompanied by a smaller concentration than the standard technique \( (P<0.02) \). It is of interest to note that, over the time period studied, spinal analgesia was accompanied by the lowest concentrations of these substrates.

**Other variables**

**Gastric aspirate.** These results were variable and inconclusive and not reported in detail. However, there was a significant increase in pH during and after operation in all groups which was accompanied by a significant decrease in volume in those patients receiving fentanyl.

**Blood loss.** This averaged \( 307 \pm 41 \) (SEM) ml in the standard group, \( 165 \pm 16 \) ml in the spinal group and \( 191 \pm 25 \) ml in the fentanyl group. The blood loss was significantly decreased \( (P<0.05) \) in supplemented groups and these did not differ significantly from each other.

**Analgesia.** Table V shows that there was a significant difference \( (P<0.002) \) between the times before the first analgesic was required in the three series, and a similar significant difference between the analgesic requirements.

<table>
<thead>
<tr>
<th>Time to first analgesia (min)</th>
<th>Papaveretum in first 24 h (mg kg(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>76</td>
</tr>
<tr>
<td>Spinal</td>
<td>239</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>358</td>
</tr>
</tbody>
</table>

**DISCUSSION**

This comprehensive study differed from other reported series in having a standard non-analgesic technique, even to the exclusion of nitrous oxide (George et al., 1974; Brandt et al., 1976; Kehlet et al., 1979).

Table VI concisely summarizes the overall changes in plasma concentrations of the hormones or biochemical variables studied. In the doses used fentanyl produced the more effective attenuation of the stress response as defined and measured in this study. However, in operations of this duration, the moderate doses of fentanyl used did have the disadvantage that prolonged respiratory depression was
observed in all the patients in that series. This may be less of a problem with other forms of anaesthesia for more prolonged operations. Some may be prepared to antagonize this depression with naloxone, but the authors did not consider this ethical, because of the coincident reversal of analgesia. In addition, naloxone is unpredictable in its duration of effect and may be followed by unexpected secondary respiratory depression.

In spite of conductive block of the afferent fibres from the operative site, spinal analgesia produced only modified blockade of the response to stress. As expected, it did not obviate the cardiovascular response to tracheal intubation. In this study, the level of sensory block was to T10 at a minimum, before general anaesthesia was induced. It is worth noting that Enquist and colleagues (1977) blocked the hyperglycaemic and cortisol responses to a similar operation with an extradural blockade extending from T4 to S5.

We have no means of knowing whether abolition or attenuation of the cardiovascular, hormonal and metabolic responses, by a suitable anaesthetic technique implies that there was a "stress-free" operative procedure.

Furthermore, one does not know whether complete attenuation is always advantageous to the patient. The cardiovascular stability which accompanies, and is probably a consequence of, the neuroendocrine blockade produced by the fentanyl technique is attractive if it can be reproduced in patients with cardiovascular disease. However, the use of this technique requires a high standard of postoperative care and a longer period in a recovery ward.

ACKNOWLEDGEMENTS

Our thanks are due to the many gynaecologists and their anaesthetic colleagues, particularly Dr J. Moore, who collaborated in obtaining these closely comparable series of patients, and to the Royal Victoria Hospital Laboratory for their biochemical estimations.

REFERENCES


une hystérectomie par voie abdominale ont été réparties au hasard
en trois groupes, intitulés Standard (anesthésie i.v. seule), Rachidi-
dien (anesthésie i.v. + rachidienne) et Fentanyl (anesthésie i.v.
plus fentanyl). Aux doses utilisées, c'est le fentanyl qui a entraîné
l'atténuation la plus efficace des réponses cardiovasculaires,
hormonales et métaboliques à l'agression mais il avait l'inconvé-
nient de provoquer une dépression respiratoire prolongée.
L'anesthésie rachidienne n'entraînait qu'un blocage modifié de la
réponse à l'agression et n'affectait pas la réponse à l'intubation.

KARDIOVASKULÄRER UND BIOCHEMISCHER
NACHWEIS VON STRESS WÄHRENDE GROSSE
CHIRURGIE BEI VERSCHIEDENEN
NARKOSETECHNIKEN

ZUSAMMENFASSUNG

Die relativen Vorzüge einer potenter narkotischen und einer
spinalen Anästhesie in ihrem Einfluss auf die Stressreaktion
durch eine Standardoperation werden verglichen. Fünf und vierzig
geeignete Patientinnen, die für abdominale Hystérectomie vor-
gesehen waren, wurden auf drei Gruppen zufällig verteilt: Stan-
dardgruppe (nur i.v.-Anästhesie), Spinalgruppe (Spinalanä-
thesie plus i.v.Anästhesie) und Fentanylgruppe (Fentanyl plus
i.v. Anaesthésie). In den verabreichten Dosen erzielte Fentanyl die
effektivste Abschwächung der kardiovaskulären, hormonellen
und metabolischen Stressreaktionen, hatte aber den Nachteil
einer verlängerten Atemdepression. Die Spinalanästhesie führte
nur zu einer mäßigen Blockierung der Stressreaktion und
beinflußte nicht die Reaktion auf die Intubation.

EVIDENCIA CARDIOVASCULAR Y BIOQUIMICA
DE LA TENSION, ASOCIADA CON DIFERENTES
TECNICAS DE ANESTESIA DURANTE LA
INTERVENCION QUIRURJICA

SUMARIO

Se evaluaron los méritos relativos de un fuerte narcótico y de un
analgésico de la columna vertebral para influenciar la respuesta de
tensión ante una intervención quirúrgica típica. Cuarenta y cinco
pacientes, dispuestos para ser intervenidos de histerectomia ab-
dominal, fueron asignados a tres grupos de forma aleatoria,
denominándose los grupos como típico (anestesia intravenosa
solamente), vertebral (anestesia intravenosa y de la columna
vertebral) y fentanilo (anestesia intravenosa más fentanilo). De las
dosis utilizadas, el fentanilo fue el que produjo la atenuación más
efectiva de las respuestas metabólicas, hormonal y cardiovascular
ante la tensión, pero presentó la desventaja de prolongar la
depresión respiratoria. La anestesia de la columna vertebral
produjo solamente un bloqueo modificado de la respuesta a la
tensión y no estorbió la respuesta a la intubación.