INDUCED HYPOTHERMIA FOR RADICAL OPERATION IN CARCINOMA OF CERVIX UTERI

BY

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The following considerations led to the operation of radical hysterectomy for carcinoma of the cervix uteri being chosen for the first essay into induced hypothermia at the Southern General Hospital, Glasgow. Even in the most expert surgical hands the stress associated with this operation is not inconsiderable, and under conventional anaesthesia the postoperative condition of these patients is often disappointing.

Smith and Fairer (1953) claimed that extensive pelvic operations could be carried out under the modification of Laborit’s technique of “hibernation anaesthesia” which they described, and that the patient’s reaction to the stress of the operation was less than by the conventional anaesthetic techniques. Also the transfusion of blood could be restricted to replacement of a volume equal to that lost, and that this loss in extensive pelvic clearances amounted to only 300–400 ml of blood (Smith and Fairer, 1953). It was also claimed that the hibernation technique could be used for poor surgical risks, even those who ordinarily would be considered unfit for major surgery under general anaesthesia (Smith and Fairer, 1953). This was supported in an Annotation in the British Journal of Anaesthesia, published in October 1953, and later received further support from Dundee and Mesham in July 1954.

The work of Dundee, Scott and Mesham (1953) describing the use of the so-called “lytic cocktail” had one important difference from that of Smith and Fairer (1953), viz. the use of lytic cocktail to facilitate the production of hypothermia in animals to which ice was applied. These animal experiments also showed that of the three constituents of the lytic cocktail, viz. chlorpromazine, promethazine and pethidine, the former was the most active agent in the induction of hypothermia.

The technique adopted at the Southern General Hospital conformed to the work of Dundee, Scott and Mesham, the lytic cocktail being administered to render the patient poikilothermic, the body temperature thereafter being reduced by means of surface cooling.

TECHNIQUE

On the evening prior to the day of operation a suitable barbiturate, usually quinalbarbitone 3 grains (180 mg) was administered orally at 7.30 p.m. followed, if necessary, at 10 p.m., by 15 grains (900 mg) each of chloral hydrate and potassium bromide. The chloral and bromide in the same dosage was repeated the following morning. In each case the patient
was scheduled to be in theatre, ready for surgery, at 2 p.m.

Two hours pre-operatively, promethazine 50 mg was administered intramuscularly, followed in one hour by pethidine 100 mg and scopolamine 0.43 mg by the same route. The patient was then transferred to the anaesthetic room which had been cooled as far as possible by shutting off the heating and opening the windows. An intravenous infusion of normal saline was set up into an arm vein to act as a vehicle and diluent for the lytic cocktail. Chlorpromazine, if injected undiluted, may damage the endothelium of the vessel wall and precipitate a thrombo-phlebitis (Dundee and Mesham, 1954; Churchill-Davidson, 1954). This same reason indicated the injection of the mixture into the drip tubing at some distance from the needle.

Chlorpromazine 50 mg, promethazine 50 mg, and pethidine 100 mg were then drawn into a 10-ml syringe, the total volume of the “mixture” of drugs, usually referred to as the “lytic cocktail”, being 6 ml. This was injected as described via the drip tubing in four divided doses, viz. 2 ml + 2 ml + 1 ml + 1 ml at 7 1/2-minute intervals, commencing half to one hour pre-operatively. Additional amounts of the mixture were given when necessary.

In view of the depression of the respiratory rate which occurred, oxygen inhalations were started soon after injection of the first 2 ml of the mixture and after the second 2 ml, thiopentone 100–250 mg and suxamethonium chloride 50 mg was administered via a vein on the back of the hand or forearm. Orotracheal intubation with a suitable Magill cuffed endotracheal tube was carried out and a wet throat pack placed in position after lubrication of the hard palate and posterior pharyngeal wall with K.Y. jelly. Maintenance thereafter was by a 50 per cent mixture of nitrous oxide and oxygen through Waters’ apparatus with soda-lime carbon dioxide absorption.

In the first three cases exposure to the room temperature was all the surface cooling attempted. Subsequently more drastic cooling was applied by the application of ice-bags to the chest wall, abdomen, axillae, and groins, the cooling effect of which were enhanced by a draught of cold air circulating round the patient.

The patient was taken into the operating theatre when the body temperature was falling satisfactorily, but since the rate of cooling was unpredictable, at first the operation tended to be anything up to 40 minutes late in starting. Although it is now found possible to have the patient ready for the surgeon at approximately the proposed time, the great drawback of the technique itself still remains, viz. the inability to control the fall in body temperature accurately to a predetermined level, and similarly the rise in temperature during rewarming.

MANAGEMENT DURING OPERATION

With the patient in position on the operating table, a polythene tube was inserted into the inferior vena cava through the saphenous vein at the groin, to be used for such transfusion as was necessary, and to act as a vehicle for further intravenous medication. Ringer-lactate solution was used until blood transfusion became necessary. The saline infusion into the arm was discontinued and the patient was then ready for operation.
The main reasons for the change from an arm vein to the inferior vena cava were firstly to expedite rapid blood transfusion should the need arise, and secondly the degree of Trendelenberg position (40°–45°, measured by a tiltometer) required by the surgeon would carry the risk of brachial plexus paralysis if an arm was maintained in 90° of abduction throughout the operation.

Muscular relaxation was provided by d-tubocurarine chloride 15–30 mg, sufficient to render the patient apnoeic, being given intravenously just before the operation commenced. In two cases it was found necessary to give a further 100 mg thiopentone at this stage. Throughout operation supplementary doses of d-tubocurarine chloride 5–10 mg were given as required. One case required thiopentone 250 mg during the operation. Manually controlled respiration was carried out, and at the end of operation residual respiratory paralysis was eliminated, if necessary, by intravenous injection of neostigmine 1–3 mg which was preceded, five minutes earlier, by an intravenous injection of atropine sulphate 0.32 mg. This sequence is preferred to including neostigmine and atropine in a single injection, a practice which does not always avoid producing bradycardia.

In order to achieve an approximately accurate replacement of the volume of blood lost, all shed blood was collected on swabs which were carefully weighed.

POSTOPERATIVE CARE

On leaving the operating theatre, the patient was covered by one sheet, and on arrival in the ward the only movement allowed was to transfer her from the theatre trolley to her bed. Oxygen at a flow of four litres per minute was administered through a nasopharyngeal catheter until it was certain that it was no longer required to ensure adequate oxygenation. The limitation of movement and administration of oxygen were precautionary, the former as a safeguard against the hypotension which may be induced by injudicious movement at the end of a prolonged abdominal operation.

Additional blankets were added if shivering occurred, the danger of the burden thrown on the cardiovascular system by shivering having been explained to those concerned. The natural reluctance of nurses to a patient being left more or less uncovered having been overcome, it was possible to indicate that the postoperative nursing care should be as for a similar operation performed under conventional general anaesthesia.

The inferior vena cava infusion was kept running at a slow rate with Ringer-lactate solution for twelve hours, not for the purpose of further fluid replacement, but as a precautionary measure lest massive reactionary bleeding during this time should necessitate immediate blood transfusion.

Apart from an indication that caution should be exercised, no restriction was placed on the prescribing of postoperative sedation by the resident medical staff. Morphine, papaveretum and pethidine were all used, although the preference of the anaesthetist was for pethidine.

Breathing exercises were introduced pre-operatively and continued postoperatively. All ten patients in this series, with the exception of No. 11 (table II), were allowed up to sit on a chair 2–4
days after operation. The exception was a pelvic exenteration carried out on September 16, 1954, after which the patient continued to bleed per vaginam, developing a vesicovaginal fistula by November 4, 1954, and a pathological fracture of the upper third of the right femur on December 19, 1954.

Apart from minor changes, the technique has been as described for all ten cases, the most important changes being that in the later cases one intramuscular injection of chlorpromazine 50 mg, promethazine 50 mg and pethidine 50 mg has been substituted in the premedication for the two injections of promethazine, and pethidine and scopolamine: also, in suitable cases rewarming is now hastened by the addition of blankets when the patient is returned to the ward.

INVESTIGATIONS AND RECORDINGS

The cardiovascular, pulmonary and renal systems were investigated pre-operatively. Recording of the blood pressure, pulse rate, respiratory rate and body temperature was begun two hours pre-operatively, and ten-minute recordings made throughout the induction period, during operation, and for one-hour postoperatively. Subsequent readings were made at fifteen-minute intervals, then at thirty-minute intervals, and finally hourly, for twenty-four hours. Rectal temperatures were taken by means of a thermocouple. Blood pressure readings were interrupted in the evening, it being thought more important that the patient should have an undisturbed sleep than that a continuous record should be obtained. The blood pressure was checked if the patient was awake at any time during the night, or if any change in the condition of the patient was suspected. The action of the heart was monitored throughout the operation by means of repeated electrocardiograph tracings, only minor changes, reversible on rewarming, being found.

COMPLICATIONS OF HYPOTHERMIA

In this series neither prolonged hypotension nor prolonged hypothermia were encountered, nor were reactive haemorrhage or postoperative anuria. One patient (table II, No. 7) was oliguric for three days after operation, but thereafter gave no further cause for anxiety. An extensive deep vein thrombosis of the left leg was developed by case No. 9 on the 11th postoperative day, but this event was not thought to be associated with the anaesthetic technique. In case No. 11 a transient mild degree of jaundice appeared the day after operation but cleared up within twenty-four hours. Case No. 16, developed a tachycardia which after persisting for three days settled without treatment. During the period of tachycardia the patient displayed occasional mental confusion.

RESULTS

There have been sixteen patients suffering from carcinoma of the cervix uteri treated by radical operation in the Southern General Hospital between April 1952 and August 1955. The first six of these had spinal analgesia plus general anaesthesia and are shown as a series numbered 1–6 in table I. The remaining ten operated on under the technique described in this paper constitute a second series numbered 7–16, as in tables II and III.
### TABLE I

**Six cases of carcinoma of the cervix uteri operated on under spinal analgesia and general anaesthesia**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Operation</th>
<th>Date of operation</th>
<th>Transfusion. Vol. in ml</th>
<th>Postoperative condition</th>
<th>Postoperative sedation, up to 72 hours (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>During op.</td>
<td>Post-op.</td>
<td>Total</td>
</tr>
<tr>
<td>1</td>
<td>51</td>
<td>Radial hysterectomy</td>
<td>16.4.52</td>
<td>1136</td>
<td>—</td>
<td>1136</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>Wertheim hysterectomy</td>
<td>22.4.52</td>
<td>1704</td>
<td>—</td>
<td>1704</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>Radial hysterectomy</td>
<td>20.8.52</td>
<td>568</td>
<td>1136</td>
<td>1704</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>Radial hysterectomy</td>
<td>13.5.53</td>
<td>1420</td>
<td>852</td>
<td>2272</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Radial hysterectomy and lymphadenectomy</td>
<td>15.12.53</td>
<td>2272</td>
<td>1136</td>
<td>3408</td>
</tr>
</tbody>
</table>
### Table II

Ten cases of carcinoma of the cervix uteri operated on under general anaesthesia potentiated by hypothermia.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Operation</th>
<th>Date of operation</th>
<th>Postoperative condition</th>
<th>Postoperative sedation up to 72 hours (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>47</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>12.2.54</td>
<td>Satisfactory on return from theatre.</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13.2.54. Night report: &quot;Condition satisfactory during night.&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.2.54. General condition excellent, but urinary output not very good.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>26.2.54</td>
<td>26.2.54. Day report: &quot;Condition satisfactory since return to ward.&quot;</td>
<td>Papaveretum 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27.2.54. Night report: &quot;Condition remains satisfactory.&quot;</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>11.5.54</td>
<td>Condition remained satisfactory until 22.5.54, when an extensive deep vein thrombosis of left leg occurred.</td>
<td>Pethidine 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Morphine 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pethidine 100</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>24.8.54</td>
<td>Condition satisfactory on return from theatre. Remained satisfactory throughout convalescence.</td>
<td>Pethidine 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Died</td>
<td>17.9.54. Day report: &quot;Slightly jaundiced otherwise satisfactory.&quot;</td>
<td>Papaveretum 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.11.54. Presence of vesico-vaginal fistula confirmed.</td>
<td>Pethidine 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.12.54. Very peaceful throughout the night. Condition satisfactory.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>54</td>
<td>Anterior exenteration</td>
<td>6.5.55</td>
<td>Uneventful convalescence.</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>17.5.55</td>
<td>Complained only of vague abdominal pain when coughing.</td>
<td>None</td>
</tr>
<tr>
<td>16</td>
<td>35</td>
<td>Radical (modified Wertheim) Hysterectomy</td>
<td>25.8.55</td>
<td>Tachycardia with occasional mental confusion until 3rd postoperative day. Subsided without treatment.</td>
<td>Pethidine 100</td>
</tr>
</tbody>
</table>
Table III shows the figures appertaining to the induction and maintenance of anaesthesia and hypothermia in cases number 7–16. Haemorrhage varied from 212 ml (Case No. 12), to 2328 ml (Case No. 11). The average volume of blood loss, as shown in table III, was 861 ml, while the average volume transfused was 1060 ml. In two cases (Nos. 7 and 9) replacement was in excess of the estimated loss owing to the reluctance of the surgeon to replace a lesser quantity, and also to some extent in other cases by the tendency to finish a bottle of blood, once started, rather than to discontinue the transfusion as soon as the estimated volume had been transfused.

Four of the ten cases required no sedation within seventy-two hours of operation and the average amount for the series over this period was equivalent to 11 mg of morphine (22 mg papaveretum = 100 mg pethidine = 11 mg morphine).

**DISCUSSION**

It is intended to assess this small series of ten cases (table II, Nos. 7–16), in order to determine if the induction of hypothermia by this technique is of advantage for the treatment of carcinoma of the cervix uteri by radical hysterectomy. Where possible, a comparison will be drawn with the earlier series (table I, Nos. 1–6), operated on under spinal analgesia and general anaesthesia, particularly in respect of the postoperative condition, sedation within seventy-two hours of operation, and blood transfusion. The average ages of the two series are, in table I, 39.5 years (31–51 years) and in table II, 46.7 years (31–62 years). In any comparison there is therefore a slight age advantage to the former group.

Those operated on under hypothermia may be subdivided with reference to the cooling which took place. The first three
cases exhibit only a mild degree of hypothermia, corresponding to the mild surface cooling effect of exposure to a cool environment as described for these cases. The remaining seven, i.e. those subjected to the application of icebags, underwent a moderate degree of hypothermia. Temperatures ranging down to 35°C are regarded as mild hypothermia, between 30°C and 35°C as moderate, and below 30°C as deep.

In so far as this operation is concerned the progression from a fall in body temperature of 1.6°C and 1.7°C to one of 6.3°C has not produced a significant difference in the postoperative condition of the various patients. The main advantage of lower temperatures seems to be in an improvement in operating conditions, due to a reduction in the amount of bleeding which takes place. There is no doubt, however, that the immediate postoperative condition of this series (Nos. 7–16), even those with a minimal fall in temperature, has been much more satisfactory than that of the first series. The latter observation receives support from the nursing staff and from the gynaecologist, both of whom would regard a return to spinal analgesia and general anaesthesia as a retrograde step.

None of the patients operated on under hypothermia died in the postoperative period. Two of the other series did succumb, one twenty-eight hours after operation, the other after twenty hours. In the latter case (No. 6), haemorrhage from a sizeable blood vessel was encountered which could only be controlled by artery forceps being left in position, the patient having to be returned to the ward with the forceps protruding from the wound. Blood transfusion amounted to 3408 ml of blood but the general condition remained poor until death occurred. The other patient (Case No. 5), in the earlier series, who died, became shocked during a prolonged and difficult pelvic exenteration. In spite of transfusion to the extent of 2272 ml of blood in theatre and 1704 ml in the ward, resuscitation was unsatisfactory.

It is noteworthy that in case No. 15, damage to the external iliac vein required it to be ligated. The ligature slipped towards the end of the operation, and the abdomen had to be re-opened. This accident became apparent before the patient had left the operating theatre. Haemorrhage was estimated at 2842 ml and transfusion to the extent of 3410 ml was carried out. The systolic blood pressure had fallen to 35 mm Hg but, with the rectal temperature at 31.2°C, the operation was performed without additional anaesthesia other than the intravenous injection of d-tubocurarine chloride, 7.5 mg. After ligation of the bleeding vessel, the blood pressure was 80/40 mm Hg, and continued to rise as the patient rewarmed.

Further recovery was uneventful, and this patient was sitting in a chair on the second postoperative day, and was allowed to walk on the fourth day.

It has already been noted that the only complications encountered which were likely to be related to the method was mild jaundice and tachycardia. Although it did not cause much anxiety in this particular instance, the former serves as a reminder that the toxicity of chlorpromazine to the liver may be of greater moment than at first believed (Courvoisier et al., 1953;
Liver damage, although perhaps not an absolute contra-indication, therefore requires careful consideration prior to embarking on the technique. No major postoperative complications related to the anaesthesia were encountered in the series conducted under hypothermia. Minor respiratory sequelae were remarkably absent.

The volume of blood lost at operation in cases Nos. 1–6 was not recorded. In this group, therefore, blood transfusion must be regarded as fulfilling the dual purpose of blood replacement and the provision of protection from operative shock. Although in the hypothermic series the extent of haemorrhage in each case is known (table III) it is obviously impractical to compare the two series with reference to haemorrhage and transfusion as a means of assessing the amount of protection from the stress of the operation afforded by the two anaesthetic techniques involved.

As noted, however, two cases (table III, Nos. 7 and 9) were overtransfused at the insistence of the surgeon. In the remaining eight cases of this series transfusion of a volume of blood equal to the loss proved adequate to maintain the patients in good general condition. This applied even in case No. 11, in which bleeding amounting to 2328 ml occurred, most of which was lost during a difficult part of the dissection in the last forty-five minutes when the stress of the operation must also have been at its maximum. The inference here is that this type of potentiated anaesthesia does provide protection from the stress of prolonged, severe operation. This is in accordance with the claims of others who have experience of hypothermia. It should perhaps be pointed out that no attempt is being made in this paper to apportion the protection afforded between the action of chlorpromazine (Smith and Fairer, 1954) and hypothermia in considering the response to stress obtained from the technique.

The dosage of anaesthetic agents in the series is also as reported by other workers, viz. a reduction in the amounts used, but as reported by Aronson et al. (1954) with respect to Smith and Fairer’s method the relaxant drugs were required in approximately the same dosage as in conventional anaesthesia (table III). It may be noted that the volume of blood lost in extensive pelvic operations, as claimed by Smith and Fairer (1953) viz. 300–400 ml under “artificial hibernation”, has not, for various reasons, been substantiated in this series, which shows average loss of 861 ml. However, a scrutiny of table III does tend to suggest that with lower temperatures, and provided no inadvertent damage to a main vessel occurs, as in case No. 11, the severity of the bleeding will be reduced.

From tables I and II it can be calculated that the average postoperative analgesia required within seventy-two hours of operation in the first series was equivalent to 55 mg morphine, compared to the equivalent of 11 mg in the second series, four of which required no sedation. With two exceptions in the second series pain was the indication in every instance. On consideration of this it would appear that the severity of postoperative pain experienced by the second series was very considerably less than in the first series. This would contribute to the absence of major respiratory complications, together with
the elimination of heavy postoperative sedation.

CONCLUSIONS

Hypothermia induced by means of the lytic cocktail and surface cooling is of some merit in the radical operation for carcinoma of the cervix uteri.

On the credit side are improved operating conditions, better postoperative condition of the patient, less pain, a reduction in sedation, comparative freedom from postoperative complications and blood transfusion reduced to a minimum. On the debit side is the appearance of one case of jaundice and one other case with a persistent tachycardia and mental confusion.

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REFERENCES