

Preemptive Analgesia by Intravenous Low-dose Ketamine and Epidural Morphine

To the Editor:—Aida *et al.*¹ present intriguing results regarding the intraoperative administration of epidural morphine combined with intravenous ketamine. However, I question their conclusion that these results provide definitive evidence for a preemptive analgesic effect. Because there was no control group to which similar doses of analgesics were administered nonpreemptively, the possibility must be considered that the results of this study were due to persistent effects of the analgesic regimen rather than a true preemptive effect.

The experimental design of this study included postoperative administration of a single intravenous dose of naloxone to the patients to whom preemptive epidural morphine had been administered. The authors postulate that this single dose of naloxone displaces the epidurally administered morphine from the spinal receptors and that the morphine present in the neuraxis is then distributed around the body. They further postulate that morphine will no longer be present in adequate concentrations to exert an analgesic effect once the naloxone has been eliminated. No evidence was provided to support this assertion.

The patients in this study to whom preemptive epidural morphine was administered without intravenous ketamine had significantly less postoperative pain than the patients to whom only postoperative

epidural morphine was administered. This result is consistent with a prolonged effect of the preemptively administered morphine. (The average dose of intraoperative epidural morphine in the preemptive group was approximately 7.7 mg.) Because of its hydrophilic nature, clearance of morphine from the cerebrospinal fluid is slow.² It seems likely that epidurally administered morphine is not rapidly redistributed after a dose of naloxone. Rather, a significant reservoir of neuraxial morphine may be expected to persist well beyond the duration of effect of the naloxone.

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Improved, but Not Preemptive, Analgesia

To the Editor:—We read with much interest the study of Aida *et al.*¹ regarding the “preemptive” analgesic effects of intravenous ketamine and epidural morphine in gastrectomy patients. The improved postoperative analgesia, particularly in the group to which both medications were administered, is certainly a useful clinical effect. However, we disagree with the authors’ use of the term preemptive analgesia to describe their results.

As noted by McQuay,² attributing improved pain control to a “preemptive analgesic” effect requires a comparison of the prestimulus (“preemptive”) therapy with an identical therapy administered after the stimulus. Comparing groups to which a prestimulus analgesic was administered with a placebo group to which no poststimulus dose was administered merely examines the effects of increasing the total dose of analgesic. The study of Aida *et al.*¹ is an example of this phenomenon. There were no groups to which equivalent poststimulus doses of either ketamine or morphine were administered.

In addition, the prolonged duration of epidural morphine (6–24 h) may have contributed to the postoperative analgesia in the epidural morphine groups. Although the authors attempted to compensate for this by administering a single dose of intravenous naloxone “after skin closure to block the continued effect of the preemptive morphine,”¹

the validity of this is based on a series of assumptions: first, that the naloxone entered the spinal cord in sufficient quantities to release all the morphine from its receptors; then, that all the morphine diffused into the systemic circulation; and finally, that the morphine was completely eliminated from the body so that it could not reenter the spinal cord and bind to its receptors when the naloxone effects dissipated. Without evidence supporting these assumptions, the possibility remains that the “preemptive” epidural morphine was still present in sufficient quantities to produce postoperative analgesia.

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When Is Preemptive Analgesia Truly Preemptive?

To the Editor:—We read with interest the article of Aida *et al.*,¹ and we wish to point out our concerns. First, the authors use the term preemptive analgesia even though they treated the three groups with

analgesics both before and after the surgical incision. Such a study design is not appropriate to demonstrate a preemptive effect because no comparison is attempted between similar analgesic interventions

applied before or after the start of the surgical stimulus.² Furthermore, before the start of the stimulus, nitrous oxide, which has a preemptive effect, was administered to all groups.³

Second, the authors report that "for definitive preemptive analgesia, blockade of opioid and *N*-methyl-D-aspartate [NMDA] receptors is necessary," and that "This mechanism (dual blockade of opioid and NMDA receptors) may account for the current results."¹ Apparently, there is a misconception because it is the activation of the opioid receptors by an agonist (and not their "blockade") that exerts an antinociceptive effect.

Third, why did the authors need a control group when their assumption could have been tested by an enhanced analgesic effect in the combination group? For the same reason, the use of naloxone is not justifiable. On the contrary, it is hard to persuade for the precise dose of naloxone required to reverse the aftereffect of epidural morphine and at the same time to allow the postoperative morphine to produce analgesia. The authors report that the naloxone administered neither increased postsurgical pain nor interfered with the postoperative morphine, but this is based on a retrospective observation. At the time of the design and conduct of the study, it would not be possible to predict the response of the patients.

Fourth, whether the vagus nerve conveys visceral true nociceptive information and to what degree remain controversial.⁴ Vagal afferent pathways may have a modulatory antinociceptive and analgesic effect, and dorsal horns and spinothalamic tracts receive vagal inhibitory influences.⁵ It seems more likely that the primary nociceptive input from the stomach comes from the afferent fibers following the sympathetic route to the dorsal horns.⁴ With regard to the effects of the gastrectomy in particular, it seems more likely that nociception and pain originates mostly from the injury to the somatic structures of the

area, rather than the viscera themselves. This nociception is predominantly conveyed by somatic afferent fibers to spinal segments, where nociceptive signals from sympathetic afferents also converge. It has been previously shown that systemically administered analgesics may potentiate the effect of other antinociceptive or analgesic agents administered neuraxially.^{6,7} Therefore, in this context, the findings could be consistent with an interactive potentiation of the epidurally administered morphine by the systemically administered ketamine.

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In Reply:—For the study of preemptive analgesia, preincisional and postincisional groups or preincisional and post-skin-closure groups are sometimes compared. Nociception at skin incision (skin pain) may have a strong impact on central sensitization, as shown by Katz *et al.*¹ However, nociception may also occur at any time during surgery, and intrasurgical nociception is also considered an important sensitizing factor (deep pain, including visceral pain). Therefore, postincisional analgesia may reduce central sensitization in control subjects. On the other hand, an analgesic administered after skin closure produces its effect after surgery, directly reducing postsurgical pain in control subjects. These observations suggest that postincisional as well as post-skin-closure groups are inadequate controls for studying preemptive analgesia. Consequently, we believed that eliminating the aftereffect of morphine in the preemptive group could be an appropriate control.

Naloxone is widely known to rapidly antagonize the effect of morphine,² and this has been clearly evidenced in clinical practice. Opioid receptors are expressed on spinal cord neurons. Regardless of administration routes, intravenous or epidural, morphine binds to spinal opioid receptors, and naloxone displaces morphine from its binding sites, also irrespective of the administration route used.

In a recent investigation, the half-life of intrathecally administered morphine was shown to be approximately 2 h. Approximately 60% of the intra-spinal cord morphine was cleared into the systemic circulation.³ In our study, naloxone administered at the end of surgery may have efficiently accelerated the clearance of morphine and shortened its half-life. Furthermore, our dosage of epidural morphine was smaller than that of intravenous morphine.⁴ The onset of naloxone's antagonistic effect is rapid, and the duration of the effect is short.² Therefore, the aftereffect of morphine might be eliminated earlier, suggesting that postsurgical pain control might be achieved smoothly and that the aftereffect of morphine might be negligible at the first observation (6 h).

In our study,⁴ a statistically significant difference between the epidural morphine and combination (epidural morphine plus intravenous ketamine) groups was observed at every time point measured (6, 12, 24, and 48 h). In contrast, a significant difference between the epidural morphine and control groups was noted only at 24 and 48 h. The significant reduction in pain intensity with epidural morphine may be due to its preemptive effect (although not definitive) rather than to its aftereffect because morphine's aftereffect must be evident at earlier time points (*i.e.*, 6 and 12 h).

Ketamine binds to *N*-methyl-D-aspartate receptors and blocks nociceptive impulses. As stated previously, morphine binds to opioid receptors and also blocks primary afferent nociception. We used the word blockade for nociceptive blockade. As pointed out by Sarantopoulos and Fassoulaki, blockade of *N*-methyl-D-aspartate receptors and stimulation of opioid receptors (dual blockade of nociception) might potentiate the preemptive analgesic effect, as mentioned in our article.⁴

On the other hand, in gastrectomy, by total nociceptive blockade (T4-L1) over the surgical area (20 ml mepivacaine, 2%, at 60-min intervals was used intermittently; blockade was verified by pin-prick test before general anesthesia), most primary afferents to the spinal cord were intercepted. However, definitive preemptive analgesia was not attained. This fact also suggests the vagal nociception in gastrectomy. However, definitive preemptive analgesia was also attained by concomitant intravenous low-dose ketamine (unpublished data).

Each group in our study received the same premedication and anesthesia. Therefore, premedicated drugs or anesthetics, including nitrous oxide, affected all groups, including the control group, equivalently. Nitrous oxide might have had an effect on nociception. However, the effect of nitrous oxide is small⁵ and may be negligible because in clinical anesthesia for surgery, analgesic intervention, such as anal-

gesia with morphine or fentanyl, or epidural block, is usually required to avoid intrasurgical reaction to nociception. Thus, central sensitization is established during anesthesia with nitrous oxide.

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Draeger Narkomed 6000 Poses Patient Safety Risks

To the Editor:—The Draeger Narkomed 6000 anesthesia delivery system (Telford, Pennsylvania) incorporates self-testing features that are designed to automate the checkout process. However, while evaluating the system (S/N 10038, software version M1/7.0) for use in our hospital, I discovered three significant deficiencies, which pose a risk to patient safety.

First, in an emergency situation, with the machine turned off, the flush valve delivers high-flow oxygen, provided there is a source of oxygen (pipeline or tank) available. However, in contrast to other machines, positive-pressure ventilation cannot be administered *via* the breathing circuit because the ventilator's built-in pressure relief valve is open under these circumstances.

Second, immediately after the system is turned on, it remains impossible to deliver positive-pressure ventilation. After filling the circuit from the flush valve or flow meters, the circuit does not hold pressure, even if the pop-off valve is completely closed. Positive-pressure ventilation can only be accomplished after the self-test procedure is completed (requiring 4 min), the self-test procedure is interrupted by pressing the standby button (requires about 33 s), or the red, emergency ventilator bypass button is pressed (requires about 13 s). In the third instance, although manual ventilation is possible, the machine must be completely reset and tested before the ventilator can be used.

Third, if the machine is turned off briefly while running on battery power (which might occur accidentally, or perhaps intentionally if it is

necessary to reset the computer) and then restarted, the computerized electronics may fail: The display first indicates "Please wait while system writes unsaved data to disk." This is followed by the message "It is now safe to turn off your computer," accompanied by a small box on the screen indicating "Restart." Touching this box causes the computer to restart, but shortly thereafter, the machine electronics abruptly power down: The screen goes dark, the fans go silent, and even the flowmeter lights switch off. Furthermore, during the abortive start-up process, there is no indication of the AC power failure. Despite this electronic failure, the flowmeters continue to operate properly because the pneumatic switch remains in the "on" position. However, manual positive-pressure ventilation may not be possible, depending on the internal state of the ventilator pressure relief valve.

I believe that these characteristics pose a significant risk to patient safety. If an electrical or electronic failure occurs, the ventilator's internal pop-off mechanism cannot be bypassed, and it is impossible to deliver positive-pressure ventilation manually with the rebreathing bag. Although internal battery backup power provides a measure of protection, a failure in the internal power supply circuitry could result in inability to provide positive-pressure ventilation. A mechanical switch-over device, similar to those used in previous anesthesia delivery systems, would reduce or eliminate the risk of these problems.

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In Reply:—Patient safety is of paramount consideration in the design of all Draeger Medical products (Telford, Pennsylvania). In his letter, Dr. Gross offers an opinion about the safety of the Narkomed 6000 that is not substantiated by data or factual evidence and is based on an incomplete understanding of the machine design. In his conclusion, Dr. Gross states that "If an electrical or electronic failure occurs, it is impossible to deliver positive-pressure ventilation manually . . ." Dr. Gross also states in his conclusion that "a failure in the internal power supply circuitry could result in inability to provide positive-pressure ventilation." Both of these statements are incorrect. In fact, even if both internal and external power sources fail, internal pneumatic controls ensure that manual ventilation is always possible, including fresh gas and anesthetic delivery, as long as the main switch is in the "on" position, and a supply of gas is available. Recognizing the possibility of power failure, this feature was a fundamental objective of the Narkomed 6000 design team from the outset of the design process. In

his letter, Dr. Gross raised three specific issues that will be addressed individually.

In his first point, Dr. Gross talks about "an emergency situation, with the machine turned off." None of the current Narkomed models are designed to be used in any situation with the machine turned off. When any current Narkomed anesthesia machine is turned on, fresh gas and anesthetic agent are immediately available as long as there is a gas supply. In the case of the Narkomed 6000, turning on the machine makes fresh gas available immediately and pressurizes the ventilator control valves needed to support manual ventilation. In the event of an emergency, it only makes sense to turn the machine on so that the flowmeters can be used to support any manner in which the machine will be used. It is not clear what type of emergency Dr. Gross envisions in which it would be desirable to use any Narkomed machine in the "off" position.

In his second point, Dr. Gross comments on the self-test process of the Narkomed 6000 ventilator and the time required to cancel this process. When the main switch on the Narkomed 6000 is turned to the

"on" position, the ventilator executes a self-test process. This is another safety feature that ensures that the ventilator is functioning properly and informs the user about any leaks or internal sensor problems. Evidence that clinicians often fail to detect machine faults, despite a recommended anesthesia machine checklist, supports the value of the automated self-test as a means to enhance detection of ventilator problems.¹ Dr. Gross is correct in observing that while the ventilator self-test process is active, it is not possible to provide manual ventilation. However, the automated self-test can be canceled at any time by pressing the standby key, in which case either manual or mechanical ventilation is possible within 30 s. If the ventilator self-test is canceled, the machine tracks the time since the last automated self-test was performed and reminds the user when another self-test should be performed. In hospitals where trauma patients or other emergencies demand immediate availability of the ventilator, the Narkomed 6000 can be left in the "on" position continuously. Standby modes for both the ventilator and the monitor are provided to suppress alarms and conserve power while keeping the machine immediately available for use.

The ventilator-bypass button to which Dr. Gross alludes (actually called the ventilator override switch) is another safety feature that is provided in the unlikely event that the ventilator controls do not respond. This button disables the electrical supply to the ventilator and, as in the case of all current Narkomed models, manual ventilation is immediately possible as long as gas pressure from either wall supply or a cylinder is available. The ventilator override switch is not intended to be used to bypass the start-up process.

In his third point, Dr. Gross describes the unlikely but not impossible scenario of the Narkomed 6000 being turned off and then on again while functioning on battery power. If the machine is turned off when using battery power, Dr. Gross is correct in his observation that a shutdown process begins, which ultimately turns off all power to the machine. This shutdown process takes approximately 4 min to complete and is designed to preserve battery power so the machine will start normally if it must be used before AC power is restored. The shutdown process cannot be interrupted after it begins so that if the Narkomed 6000 is turned on before the shutdown process is completed, although the ventilator will start its self-test process, monitoring functions will not be available, and all power will be turned off when the shutdown process concludes. Dr. Gross is not correct, however, in his statement that "manual positive-pressure ventilation may not be possible" in this situation. If battery power is available when the main switch is turned to "on," the ventilator begins its usual

start-up process, which can be allowed to proceed or can be canceled as described previously. If all electrical power to the machine shuts off at the conclusion of the shutdown process, manual ventilation is always immediately available as long as the main switch is in the "on" position and there is a supply of gas to the machine.

Although Dr. Gross does not define what he considers to be an emergency in his letter, I assume from his comments he is referring to a situation in which manual ventilation is required. The Narkomed 6000 is designed with many safety features that can be used in such an emergency. Like any current-model Narkomed anesthesia machine, the Narkomed 6000 is designed always to allow for manual ventilation independent of whether electrical power is available. Even if AC power fails and the batteries have been drained, as long as the main switch is in the "on" position and there is a supply of gas, pneumatic controls ensure that manual ventilation is possible. Furthermore, every Narkomed 6000 is equipped with an auxiliary oxygen flowmeter that supplies oxygen independent of whether the machine is turned on. Both prudent practice and the Food and Drug Administration Anesthesia Apparatus Checkout Recommendation dictate that an alternative means of ventilation, such as a self-inflating bag, be readily available in all anesthetizing locations.* Such a device can be connected to the auxiliary oxygen flowmeter on the Narkomed 6000 to deliver oxygen to a patient irrespective of the state of the anesthesia machine.

The Narkomed 6000 is an evolutionary computer-based anesthesia workstation that brings a number of advanced monitoring and ventilation capabilities to the operating room while still supporting manual ventilation, including gas and vapor delivery, in the event of a total electronic failure. Like any sophisticated medical device, using the Narkomed 6000 effectively requires proper training and education. The opinion expressed by Dr. Gross about the safety of the Divan ventilator and the Narkomed 6000 is based on an incomplete understanding of the machine design. Furthermore, with more than 8,000 Divan ventilators in use on Draeger Medical products worldwide and more than 500 Narkomed 6000 workstations in use in North America, his opinion is contrary to clinical experience. However, Draeger Medical appreciates the opportunity to explain the emphasis on safety that underlies the Narkomed 6000 design.

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Ventilator Failure during Use of a New Anesthesia Machine

To the Editor:—Our department recently installed new North American Draeger Narkomed 6000 anesthesia machines (Telford, PA). These are microprocessor controlled and software driven and use an internal flow-dependent, piston-driven ventilator instead of a bellows. Thorough in-service education was done before use. Within a month, we experienced an unusual but significant problem with the ventilator. Neither the cause nor the solution was obvious or intuitive, thus prompting this letter.

In a patient requiring bronchial blockade for one-lung ventilation, we planned bronchoscopy using an Olympus LF-2 fiberoptic bronchoscope (Olympus, Lake Success, NY) and a Portex swivel adapter (Concord/Portex, Keene, NH). While maintaining mechanical ventilation, secretions were suctioned from the trachea *via* the swivel adapter using a 14-French Kendall-Curity suction catheter (Kendall-Curity,

Mansfield, MA). After bronchoscope insertion, the Apnea-Low Pressure alarm sounded in response to the deliberate leak. However, it became apparent by observation of the patient and machine that there was no effective ventilation occurring. The reservoir bag was grossly distended and would not empty, the display panel read "resetting piston," the control switches were unresponsive, and we were unable to convert to manual ventilation. We disconnected the circuit and finished the procedure while maintaining ventilation with an Ambu bag. We then opened the locking lever under the ventilator cover, pulled up the ventilator and piston components, and reseated them. The piston reset itself, and the ventilator function resumed according to the original settings. The procedure continued uneventfully.

North American Draeger technical support was consulted, the problem was successfully recreated, and the cause was defined: The use of

suction in the airway during mechanical ventilation generates negative-pressure flows of approximately 30 l/min, causing the piston to empty and lock, shutting down the ventilator. In addition to deliberate airway suctioning, unintentional placement of a nasogastric tube in the trachea or negative pressure from chest tubes put to suction with the chest closed in the presence of a large bronchopleural communication may also produce this problem. The flow rate through the bronchoscope suction port was measured at only 4.6 l/min (at -375 mmHg wall suction)—a flow inadequate to cause the malfunction. Flow rates in larger bronchoscopes were not tested. The solution to this situation requires the maneuver described. By breaking the vacuum seal, the piston is allowed to reset. The mechanical ventilation override control present on this machine does not work in this situation.

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In Reply:—In their letter, Drs. Barahal and Sims describe a situation in which suction to the patient's airway before bronchoscopy caused a problem with the Narkomed 6000 ventilator (Draeger Medical Inc., Telford, PA). Draeger Medical Inc. investigated this problem and would like to describe the findings and the results of the investigation.

When the clinical circumstances of this event were recreated, it was determined that a negative pressure of -375 mmHg was applied to the airway through a 14-French suction catheter drawing a flow of 30 l/min through the catheter. When the same suction level was applied through the bronchoscope suction port, only 4.6 l/min of flow was drawn through the port, and the problem could not be recreated. Therefore, it seems that the initial airway suctioning was the inciting event, not the suction through the bronchoscope.

The problem described by Drs. Barahal and Sims occurred when a relatively high negative pressure, resulting in a high degree of suction flow, was applied to the patient's airway during ventilation. If the suction flow is high enough, it will exceed the capacity of the ventilator's negative-pressure relief system. The resulting negative pressure in the breathing system holds the diaphragm control valves closed in such a way that gas cannot enter the breathing system and relieve the negative pressure. A similar situation was reported to Draeger Medical Inc. by another institution where a high degree of negative pressure was applied to the airway through a misplaced nasogastric tube.

Typical clinical guidelines for suction applied to the adult airway recommend that suction pressure be set as low as possible to clear secretions effectively. Desirable suction levels in the range of -100 to -150 mmHg applied for up to 15 s have been cited.¹ American Society for Testing and Materials standard F960 governing Medical and Surgical Suction and Drainage Systems offers a maximum static vacuum level of -160 mmHg for adult tracheal suctioning as a guideline.² When the suction regulator used by Drs. Barahal and Sims was adjusted to

In this case, the patient was unharmed. In review, we make the following recommendations: (1) awareness of the causes and avoidance where possible; (2) switching to manual ventilation and filling the reservoir bag before airway suctioning; (3) availability of an Ambu bag to simplify the circuit if a ventilator problem occurs; and (4) machine function and problem-solving education. Routine procedures may trigger new problems when performed with new equipment. We recognize that the benefits of new technology can be tempered by their complexities and our limited ability to achieve intuitive solutions when those problems occur.

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-120 mmHg, 18 l/m of flow was drawn through the 14-French suction catheter, and the ventilator problem could not be made to occur.

Draeger Medical has taken a number of steps to address this issue. Draeger recommends that regulated suction within the range of typical clinical guidelines be used either when applying suction to the airway or at the time of initial placement of a nasogastric tube before proper placement has been confirmed. We agree with Drs. Barahal and Sims that it is prudent to put the ventilator into "manual" mode and to fill the reservoir bag before applying suction to the airway (or to a gastric tube that may be in the airway). If the reservoir bag empties as suction is applied, suction should be stopped before the bag is completely empty to avoid exposing the breathing circuit to excessive negative pressure. Draeger has also incorporated a help feature into the Narkomed 6000, which appears automatically on the monitor display should this event occur. The help feature guides the user through the simple steps that must be taken to ensure the patient's safety. Draeger has taken steps to enhance the training process to ensure that all users are made aware of the recommended degree of suction that should be applied to the airway. Finally, changes to the operator's manual will more clearly describe this situation and the strategies for avoidance.

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Positioning of Infants in the Prone Position: A Useful Technique

To the Editor:—We wish to report a useful technique for positioning infants requiring surgery in the prone position, using a commonly available adult Scheie headrest (fig. 1; Sunrise Medical, part No. 8815, Baldwyn, MS). After anesthetic induction *etc.*, the infant's torso is placed prone in the concave cavity of the headrest, and the head is supported on a soft foam, gel, or surgical headrest (fig. 2). Because the

base of the device is flat, it provides a stable support that will not slip or move as occurs if cloth or foam rolls are used. The polyurethane foam is rigid enough to support the infant, but pliable enough not to compress the tissues. The T-shaped cutout allows free movement of the abdomen, avoiding compression and secondary venous congestion.

This technique is useful for procedures on both the lower and the upper back, as well as the posterior fossa of the skull. For cervical spine or posterior fossa operations, the neck can easily be flexed by

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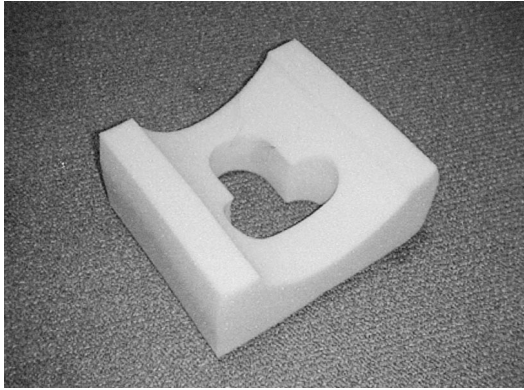


Fig. 1. Scheie Headrest (Sunrise Medical, Baldwin, MS).

elevating the support. The arms may be positioned at the infant's side or along the head, depending on the site of the operation. Padding should be used for the extremities as needed.

Monitor cables are directed away from the site of surgery. A forced-air heater may be placed above or below the device to facilitate temperature control. The technique is useful for any infant who fits comfortably in the cradle.

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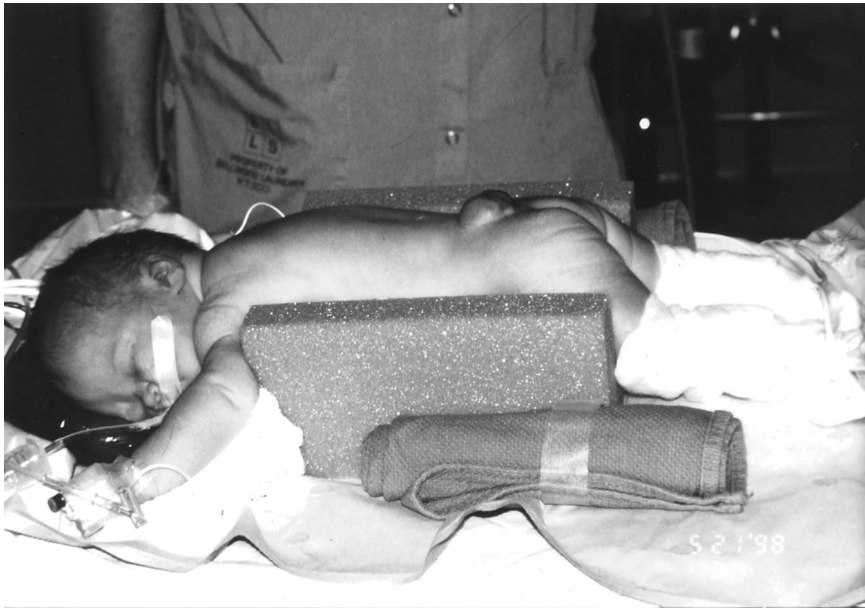


Fig. 2. Infant positioned on headrest.