Open Journal of Anesthesiology, **2014, 4, 13-30**
Published Online January 2014 (http://www.scirp.org/journal/ojanes)
http://dx.doi.org/10.4236/ojanes.2014.41003

Combined Spinal Epidural Catheters for Epidural Cooling, Cerebrospinal Fluid Aspiration and Spinal Intralipid Infusion for Treatment of Spinal and Brain Injuries, Diseases and Protection

Joseph Eldor

Theoretical Medicine Institute, Jerusalem, Israel.
Email: csen_international@csen.com

Received November 8th, 2013; revised December 13th, 2013; accepted January 13th, 2014

ABSTRACT

A new proposal for spinal cord and brain treatment and protection due to injuries and diseases is made herein. It is composed of two 20G nylon catheters with 6 lateral holes arranged circumferentially within 3 cm from the tip and a closed end. One catheter is inserted into the epidural space and the other catheter is inserted into the spinal space in two different lumbar interspaces using an 18G Tuohy needle 90 mm. The epidural catheter is used for cooled saline injection and infusion. The spinal catheter is used for Intralipid spinal injections and CSF aspiration. The proposal is based on the current studies on spinal cord cooling and CSF aspiration as well as on the Intralipid resuscitation properties and lipid brain protection. A study is needed to evaluate the clinical value of this combined approach.

KEYWORDS

Spinal Catheter; Epidural Catheter; Epidural Cooling; Spinal Intralipid; Spinal Injury; Brain Injury; Spinal Disease; Brain Disease; Spinal Protection; Brain Protection

1. Introduction

Following a traumatic injury to the central nervous system, a cascade of physiological events leads to neuronal loss including, for example, an inflammatory immune response and excitotoxicity. Despite advances in spinal cord protection, paraplegia continues to be a serious complication of descending and thoraco-abdominal aortic operations. Damage to the nervous system may result from a traumatic injury, such as penetrating trauma or blunt trauma, or a disease or disorder including, but not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), diabetic neuropathy, senile dementia, stroke and ischemia. During the past 9 years, considerable new evidence has accumulated supporting the use of prophylactic hypothermia for traumatic brain injury (TBI). In 1998 it was first showed that intravenous intralipid could prevent or improve resuscitation from cardiovascular collapse by severe bupivacaine overdose in rats. Since then published examples now include toxicities related to verapamil, diltiazem, amlodipine, quetiapine and sertraline, haloperidol, lamotrigine, olanzapine, propranolol, atenolol, nevibolol, doxepin, dosulepin, imipramine, amitriptyline, glyosphate herbicide, flecainide, venlafaxine, moxidectin, and others.

A new multimodal proposal for spinal cord and brain treatment and protection due to injuries and diseases is made herein.

2. CSF Role in Ischemic Injury

In ischemic injury, CSF has a toxic effect of facilitating cerebral edema. While intracellularly excessive water

content is directly toxic to the CNS cells, the cerebral edema can also block cerebral blood flow and collateral circulation to damaged nerve tissue, causing "no reflow" phenomenon or "hypoperfusion". This failure of circulation results in continuing damage to CNS tissue after the interruption of blood flow is reversed leading to irreversible damage. Restoration of blood flow to the affected area of the CNS after a period of complete ischemia as short as six minutes does not result in blood reflow to the affected CNS tissue. After the CNS tissue is injured by an initiating insult, such as ischemia, trauma, the CSF infiltrates the CNS tissue through water channels on the injured cell membrane to cause edema. Swelling of the tissue makes the Virchow-Robin space (also known as the perivascular space or extracellular space) smaller and may even cause it to collapse, thereby compressing the small blood vessels and resulting in an obstruction of the blood flow, such as a "hypoperfusion" or even "no-reflow" phenomenon, which prolongs the original ischemic duration, blocks collateral circulation and induces a feedback loop. As the duration of blood flow interruption increases, the edema spreads throughout the CNS tissue causing additional damage in an ischemic cascade.

In the adult human, the average intra-cranial volume is about 1700 ml. The volume of the brain is approximately 1400 ml; CSF volume ranges from about 52 to 160 ml (mean 140 ml), and blood volume is about 150 ml. Thus the CSF occupies about 10 percent of the intra-cranial and intra-spinal volume.

The choroid plexuses are the main sites of CSF formation. The average rate of CSF formation is about 21 to 22 ml/hr, or approximately 500 ml/day. The CSF as a whole is renewed four or five times daily. CSF formation is related to intracranial pressure. When the intracranial pressure is below about 70 mm H_2O, CSF is not absorbed, and production increasrs. CSF is a very dilute aqueous solution with a low colloidal osmotic pressure.

The CSF has a mechanical function. It serves as a kind of water jacket for the spinal cord and brain, protecting them from trauma and acute changes in venous blood pressure. The CSF provides buoyancy and shock absorption, so that brain and spinal cord float in a CSF pool. CSF does not appear to be necessary to brain or spinal cord metabolism. However, during ischemic episodes, CSF has a toxic effect by facilitating cerebral edema and resulting in no-reflow phenomenon after disruption of blood flow to CNS tissue.

In order to prevent cerebral edema, and the irreversible effects that occur after the CNS injuries, the CSF is withdrawn from the affected area of the CNS. It is preferred to completely remove all CSF. However, it is very difficult, almost impossible, mechanically to remove CSF completely from the subarachnoid spaces because the CNS (*i.e.* brain and spinal cord) contour is very complex with many sulci, gyri and pools.

CSF pressure control has been used for protecting spinal cord during aortic surgery. It is said that controlling the pressure of CSF, in particular, maintaining a pressure lower than the central venous pressure could be advantageous in protecting the spinal cord from injury during aortic surgery. However, such pressure control does not achieve the neuroprotective effect in the case of more general ischemia. Removing CSF from the spinal cord's subarachnoid space is relatively easier (compared with the brain) because of spinal cord's simpler contour. However, simple withdrawal of CSF even under controlled conditions in thoraco-aortic surgery, is not predictably effective protecting CSF tissue.

After the CSF has been withdrawn. The injured CNS tissue is washed with washing solutions. The first washing solution is an emulsion. It should contain oil, an osmotic agent, water and at least one emulsifier. Typically, the emulsion contains up to about 31% - 80% oil. Generally a water in oil emulsion is preferred. However, oil in water emulsions have also been effective. Intralipid solutions (10%, 20% and 30%), used clinically for parenteral nutrition, such as those manufactured and distributed by Baxter, Fresenius Kabi, Pharmacia & Upjohn etc. may also be effective. The first washing solution acts as a hook to pull out edematous CSF fluids away from the CNS tissue into the oil. The oil can be any non-toxic, organic liquid. Hydrocarbon oils and silicone oils are effective. Any hydrocarbon oils from plant, animal sources and mineral oil such as soybean oil, cod liver oil, vitamin E oil, canola oil, corn oil, and mixtures of these oils in any concentration ratio may be used [1].

3. Traumatic Injury to the Central Nervous System

Following a traumatic injury to the central nervous system, a cascade of physiological events leads to neuronal loss including, for example, an inflammatory immune response and excitotoxicity resulting from the initial impact disrupting the glutamate, acetylcholine, cholinergic, $GABA_A$, and NMDA receptor systems. In addition, the traumatic CNS injury is frequently followed by brain and/or spinal cord edema that enhances the cascade of injury and leads to further secondary cell death and increased patient mortality. Methods are needed for the *in vivo* treatment of traumatic CNS injuries that are successful at providing subsequent trophic support to remaining central nervous system tissue, and thus enhancing functional repair and recovery, under the complex physiological cascade of events which follow the initial insult [2].

The nervous system comprises the central (CNS) and the peripheral nervous system (PNS). The CNS is composed of the brain, spinal cord and visual system; the PNS consists of all of the other neural elements, namely the nerves and ganglia outside of the brain and spinal cord. Damage to the nervous system may result from a traumatic injury, such as penetrating trauma or blunt trauma, or a disease or disorder including, but not limited to, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), diabetic neuropathy, senile dementia, stroke and ischemia. Maintenance of CNS integrity is a complex "balancing act" in which compromises are struck with the immune system. In most tissues, the immune system plays an essential part in protection, repair, and healing. In the CNS, because of its unique immune privilege, immunological reactions are relatively limited. A growing body of evidence indicates that the failure of the mammalian CNS to achieve functional recovery after injury reflects an ineffective dialog between the damaged tissue and the immune system [3].

The predominant mechanism in most cases of traumatic brain injury (TBI) is diffuse axonal injury [4]. While axonal injury is common in all TBI regardless of severity, a shearing of the axons occurs in human diffuse axonal injury (DAI) leading to progressive changes that ultimately may result in the loss of connections between nerve cells. The slow progression of events in DAI continues for up to several weeks after injury creating a window of opportunity for therapeutic intervention. There are approximately 500,000 new cases of TBI in the U.S. each year [5], and the incidence requiring hospitalization is estimated to be approximately 200-225/100,000 population. Currently, it is estimated that brain injuries account for 12% of all hospital admissions in the United States [6]. When compared to spinal cord injury, which accounts for less than 1% of hospital admissions, it is clear that TBI is a medical care problem which has a significant impact financially within the United States. Approximately 30,000 - 44,000 people will survive a severe TBI with GCS score TBI (GCS#10). Yet with new medical management techniques, less than 10% will remain in a persistent vegetative state. A GCS score of eight or less generally reflects a state of unconsciousness in which the patient demonstrates no eye opening, does not follow simple commands to move muscles, and has vocalizations which are limited to sounds. Such signs are indicative of severe brain injury [7]. Approximately 52,000 to 56,000 people die each year from TBI [8], resulting in direct costs approximated at more than $50 billion annually [9]. The costs of severe TBI to the individual and family are extremely high [10]. Acute medical and rehabilitation bills are often around $100,000 with some considerably higher. The Model Systems Database for Traumatic Brain Injury demonstrates there is a correlation between the average Disability Rating Score and the combined acute care and rehabilitation charges [11]. Those with a severe TBI (GCS score of 6 - 8) have average combined charges of $110,842, and those with a very severe TBI (GCS score 3 - 5) have average combined charges of $154,256 [12]. About one-half of all TBIs are transportation related and these patients have some of the highest combined charges for acute care and rehabilitations. This may be related to the mechanism of TBI in high speed motor vehicle crashes, specifically the presence of diffuse axonal injury (DAI) being most prevalent in the midbrain and brain stem areas. Clearly, brain injuries of this severity that occur with high speed acceleration-deceleration injuries, have the highest costs to society. TBI clearly causes more mortality, morbidity and probably more economic loss than HIV infection in the United States. Motor vehicle crashes of all types are responsible for approximately 40% - 50% of the TBI admissions recorded in the Model TBI Systems Database. The predominant mechanism of injury is considered to be diffuse axonal injury (DAI). Approximately 30% - 40% of the fatal head injuries involve diffuse axonal injury by pathological examination [13]. However, based on beta-amyloid precursor protein immunostaining, axonal injury may be present in all cases of fatal head injury. In cases of persistent vegetative states, recently found that all cases had evidence of DAI in magnetic resonance imaging (MRI). Diffuse axonal injury occurs even in the absence of a blow to the head and is more prevalent than previously realized. Even in mild head injury, diffuse axonal injury is present in almost 1/3 of the cases. The defining characteristic of DAI is the morphologic change to the axons which occurs over the course of several days to weeks and the fact that multiple regions of the brain are injured. While a component of DAI is present in blunt or penetrating trauma injury, it is at the periphery of the injury zone and is much less significant than the predominant mechanism of injury. DAI is the major mechanism of injury in high speed acceleration-deceleration injuries associated with motor vehicle crashes. While all four mechanisms of TBI (DAI, blunt trauma, penetrating trauma, axonia) may be involved in such an injury, it is the predominant mechanism of injury under this condition [14].

4. Inadvertent Intralipid Spinal-Epidural Injection

A term female infant was admitted to the intensive care unit with the diagnosis of tetralogy of Fallot with critical pulmonary stenosis. On the seventh day of life a long saphenous line was inserted that remained without com-

plications until seven days later when the infant appeared septic. A lumbar puncture demonstrated the presence of intra-lipid in the cerebrospinal fluid that was interpreted as due to migration of the saphenous catheter. The child had an uneventful recovery [15].

A patient had accidently received 300 ml of intralipid total parenteral nutrition solution via his epidural catheter. A 21-yr-old man with ulcerative colitis underwent a total colectomy. Postoperative pain control was begun with intravenous morphine using a patient-controlled analgesia device. The patient was unable to obtain satisfactory pain relief. A lumbar epidural catheter was placed, and he received excellent analgesia after 100 microgram of fentanyl was injected into the epidural space. A continuous epidural infusion of preservative-free morphine at 1.0 mg/h was then begun using a standard intravenous infusion set connected to the epidural catheter tubing. The tubing and intravenous infusion pump was labeled with bright green "EPIDURAL CATHETER" tags. He remained nearly pain-free for the next 24 h. It was then discovered that an intravenous infusion of intralipid total parenteral nutrition solution had been "piggy-backed" onto the intravenous tubing leading to the epidural catheter. The label covering one of the side ports on the infusion set tubing had apparently been lost. Approximately 300 ml of intralipid solution had been infused at a rate of 60 ml/h. The epidural catheter was removed from the patient. The catheter insertion site appeared normal and was not painful to palpation. Daily visits failed to reveal any neurological deficits caused by this unusual infusion. The epidural site remained normal. There is no known reports of a similar accidental epidural intralipid infusion [16].

5. Epidural Saline Infusion

A 30-year-old female with a 4-month history of post-lumbar puncture headache (PLPHA) resulting from an accidental dural puncture during an attempted epidural anesthetic for cesarean section. Epidural blood patches were attempted at 4 days and 3 months post-lumbar puncture, but were unsuccessful. At 4 months post-lumbar puncture, a 24-h epidural saline infusion relieved the PLPHA for 48 h, but the headache returned. Finally, a second epidural saline infusion was done, followed by an epidural blood patch, which permanently cured the PLPHA. Follow-up to 4 months showed no return of the PLPHA [17].

Concerns have been expressed about the potential danger of an autologous epidural blood patch for the treatment of post-dural puncture headache. The immediate resolution of the headache with a blood patch is attributable to thecal compression raising the CSF pressure. An epidural injection of saline would, in theory, produce the same mass effect, and restore normal CSF dynamics. As saline is a relatively inert and sterile solution, epidural saline bolus or infusion appears to be an attractive alternative. Regimens that have been advocated include: 1) 1.0 - 1.5 liter of epidural Hartman solution over 24 h, starting on the first day after dural puncture; 2) up to 35 $ml \cdot h^{-1}$ of epidural saline or Hartman solution for 24 - 48 h, or after development of the headache; 3) a single 30 ml bolus of epidural saline after development of headache; and 4) 10 - 120 ml of saline injected as a bolus via the caudal epidural space.

Advocates of an epidural saline bolus or infusion maintain that the lumbar injection of saline raises epidural and intrathecal pressure. Reduction in the leak would allow the dura to repair. However, observations of the pressures produced in the subarachnoid and epidural space show that, despite a large rise in epidural pressure, the consequent rise in subarachnoid pressure maintains the differential pressure across the dura. The pressure rise is also not sustained and is dissipated within 10 min. The saline may induce an inflammatory reaction within the epidural space, promoting closure of the dural perforation. Histological studies have not demonstrated an inflammatory response following epidural Dextran 40 administration, however, in contrast to an autologous blood patch. There is no reason to suppose that epidural saline is more likely to accelerate dural healing through a pro-inflammatory action than Dextran 40. Thus, there are no studies that are able to demonstrate either a sustained rise in CSF pressure or accelerated closure of the dural perforation after the administration of epidural saline. Whilst there are many case reports describing the success of epidural saline, comparative trials with epidural blood patches have not demonstrated the long-term efficacy of epidural saline placement. It is difficult to conclude from the evidence therefore, that epidural saline administration will restore normal CSF dynamics. The administration of large volumes of epidural saline may result in intraocular haemorrhages through a precipitous rise in intracranial pressure [18].

6. Paraplegia—A Serious Complication of Descending and Thoraco-Abdominal Aortic Operations

Despite advances in spinal cord protection, paraplegia continues to be a serious complication of descending and thoraco-abdominal aortic operations. A novel, self-contained catheter designed to cool the spinal cord topically after being threaded into the spinal column. A cooling catheter for this purpose was specifically designed and produced. The catheter has two lumina, one for ingress and one for egress of fluid. The system is self-contained, so that the fluid does not communicate in any way with

the spinal fluid. A console device circulates cold fluid through the catheter. The catheter was tested in 5 adult sheep, with direct monitoring of core body temperature and spinal cord temperature in both active cooling and passive re-warming cycles. In testing in 4 sheep (five attempted implants, with one failure), the catheter worked without problem, producing effective cooling of the spinal cord, from a mean temperature of 36.8˚C (core temperature) to 30.5˚C (spinal temperature) ($p < 0.0001$). In no case did post-mortem examination or histology reveal any evidence of damage to the spinal cord from hypothermia. Temperature rose toward body temperature after cessation of active cooling. Effective topical cooling of the spinal cord can be achieved via a specially designed, self-contained cooling catheter placed into the intra-thecal space. This catheter holds promise for spinal cord protection in aortic surgery. Also, this catheter may be useful as well in mitigating injury to the spinal cord in cases of traumatic spinal column injury [19].

Paraplegia or paraparesis after otherwise successful thoracic or thoraco-abdominal aortic reconstruction is a devastating complication for both patient and physician. Various strategies have been developed to minimize the incidence of neurological complications after aortic surgery. The incidence of spinal cord ischemia and subsequent neurological complications has been correlated with 1) the duration and severity of ischemia, 2) failure to establish a spinal cord blood supply, and 3) reperfusion injury. Preoperative identification of the arteria radicularis magna, the artery of Adamkiewicz, facilitates identification of critical intercostal vessels for reimplantation, resulting in reestablishing spinal cord blood flow. Techniques for monitoring spinal cord function using evoked potentials have been developed, and surgical techniques have evolved to reduce the duration of ischemia. Furthermore, sequentially sacrificing all the intercostal arteries while maintaining collateral circulation to the cord has produced good outcomes. The severity of ischemia can be minimized by using cerebrospinal fluid drainage, hypothermia, distal bypass, managing the blood pressure, and adjunctive pharmacological therapy. Reperfusion injury can be reduced with the use of antioxidant therapy. Recent advances in endovascular stent grafting have reduced the incidence of postoperative spinal complications, especially among high-risk patients [20].

7. Hypothermia for Prevention of Paraplegia Associated with Thoracic Aortic Surgery

The most dreaded complication associated with thoracic aortic surgery remains paraplegia caused by spinal cord ischemia. The existence of this problem has been known since the early days of aortic surgery and much research, both clinical and experimental, has been devoted to the understanding and prevention of spinal cord injury. Intraoperative and peri-operative adjuncts have included both pharmacological and surgical approaches. Varying degrees of success have been reported for each new approach, with some remedies coming and going in and out of fashion as continued research either supports or refutes their effectiveness. Rather than finding any one therapy that completely removes the threat of peri-operative spinal cord injury, incremental improvements in surgical and anesthetic regimens have greatly reduced the incidence of this complication to an acceptable level.

Among the earliest adjuncts used in the battle against paraplegia was hypothermia. In studies dating back 50 years, Pontius and colleagues demonstrated that systemic hypothermia successfully allowed prolongation of the spinal cord ischemic interval in laboratory dogs [1]. For many years, the combination of moderate hypothermia, coupled with rapid surgical techniques, remained the mainstay of protection in aortic surgery. As more complex and extensive operations were attempted, profound hypothermic and circulatory arrest approaches were introduced, but for less comprehensive repairs this was thought to be overkill and was selectively used.

Hypothermic techniques, even when applied systemically in moderate or mild amounts, can adversely affect the conduct of the surgery. Prolonged operating times due to cooling and warming, the need for heaters and coolers in the circuits, and increased bleeding tendencies have all given pause to surgeons unfamiliar with these problems. Because of these issues, investigations were turned to eliminating the need for systemic hypothermia and limiting the cooling efforts to those tissues most directly affected, namely the spinal cord. Locally applied cooling blankets and appliances were found not to be effective due to the rapid rewarming by surrounding tissues and interference with the sterile fields of the procedure. Administration of iced saline solutions directly into the isolated aorta was shown to effect cooling of the spinal cord but, as one might expect, this was abandoned due to its complexity.

A more direct approach began to be explored experimentally; by installing a perfusion and drainage catheter system into the epidural or intrathecal spaces, localized sustained regional cooling could be generated. The necessity to perform a laminectomy to install this cooling apparatus as well as the direct installation of iced fluids into the epidural space made it unsuitable for aortic surgery, but alternative localized approaches continue to be explored [21].

8. Epidural Cooling Catheter to Protect the Spinal Cord from Ischemia during Aortic Surgery

Using swine, Mori *et al.* [22] investigated whether epi-

dural placement of a cooling catheter rather than infusing iced saline solution could protect the spinal cord from ischemia during aortic surgery.

Fourteen domestic pigs were divided into two groups of 7 each. Each underwent epidural catheter placement preceding 30 minutes of aortic cross-clamping distal to the origin of the left subclavian artery. In group 1, cold water was circulated continuously through the lumen of the catheter connected to an external unit. In group 2, animals received catheter placement without cooling. Spinal cord somatosensory evoked potentials were recorded. Neurologic status involving hind limbs was graded sequentially after surgery. At aortic cross-clamping, spinal temperature in group 1 (31.7˚C ± 0.6˚C) was significantly lower than in group 2 (37.8˚C ± 0.4˚C; $p < 0.0001$). No significant elevation of intrathecal pressure accompanied cooling with the catheter (group 1, 8.1 ± 1.7 mm Hg; group 2, 8.0 ± 1.5 mm Hg). Mean duration of total loss of potentials was significantly shorter in group 1 (7.4 ± 3.8 minutes) than group 2 (19.7 ± 7.3 minutes; $p = 0.0002$). Pigs in group 1 exhibited better hind limb function recovery (mean Tarlov score, 4.7 ± 0.5) than group 2 (0.6 ± 0.8; $p = 0.0017$). Group 1 showed normal histologic characteristics, whereas group 2 showed loss of motor neurons in the ventral horns. Epidural cooling catheter without iced saline infusion can cool the spinal cord without elevating intrathecal pressure, protecting the cord against ischemia [23].

Cambria *et al.* [23] summarized their experience with epidural cooling (EC) to achieve regional spinal cord hypothermia and thereby decrease the risk of spinal cord ischemic injury during the course of descending thoracic aneurysm (TA) and thoraco-abdominal aneurysm (TAA) repair.

During the interval July 1993 to Dec. 1995, 70 patients underwent TA (n = 9, 13%) or TAA (n = 61) (type I, 24 [34%], type II, 11 [15%], type III, 26 [37%]) repair using the EC technique. The latter was accomplished by continuous infusion of normal saline (4 degrees C) into a T11-12 epidural catheter; an intrathecal catheter was placed at the L3-4 level for monitoring of cerebrospinal fluid temperature (CSFT) and pressure (CSFP). All operations (one exception, atrio-femoral bypass) were performed with the clamp-and-sew technique, and 50% of patients had preservation of intercostal vessels at proximal or distal anastomoses (30%) or by separate inclusion button (20%). Neurologic outcome was compared with a published predictive model for the incidence of neurologic deficits after TAA repair and with a matched (Type IV excluded) consecutive, control group (n = 55) who underwent TAA repair in the period 1990 to 1993 before use of EC.

EC was successful in all patients, with a 1442 ± 718 ml mean (range, 200 to 3500 ml) volume of infusate; CSFT was reduced to a mean of 24 degrees ± 3 degrees C during aortic cross-clamping with maintenance of core temperature of 34 ± 0.8 degrees C. Mean CSFP increased from baseline values of 13 ± 8 mm Hg to 31 ± 6 mm Hg during cross-clamp. Seven patients (10%) died within 60 days of surgery, but all survived long enough for evaluation of neurologic deficits. The EC group and control group were well-matched with respect to mean age, incidence of acute presentations/aortic dissection/aneurysm rupture, TAA type distribution, and aortic cross-clamp times. Two lower extremity neurologic deficits (2.9%) were observed in the EC patients and 13 (23%) in the control group ($p < 0.0001$). Observed and predicted deficits in the EC patients were 2.9% and 20.0% ($p = 0.001$), and for the control group 23% and 17.8% ($p = 0.48$). In considering EC and control patients (n = 115), variables associated with postoperative neurologic deficit were prolonged (>60 min) visceral aortic cross-clamp time (relative risk, 4.4; 95% CI, 1.2 to 16.5; $p = 0.02$) and lack of epidural cooling (relative risk, 9.8; 95% CI, 2 to 48; $p = 0.005$).

EC is a safe and effective technique to increase the ischemic tolerance of the spinal cord during TA or TAA repair. When used in conjunction with a clamp-and-sew technique and a strategy of selective intercostal reanastomosis, EC has significantly reduced the incidence of neurologic deficits after TAA repair.

Despite advances in spinal cord protection, paraplegia continues to be a serious complication of descending and thoraco-abdominal aortic operations. Moomiaie *et al.* [24] devised and tested a novel, self-contained catheter designed to cool the spinal cord topically after being threaded into the spinal column. A cooling catheter for this purpose was specifically designed and produced. The catheter has two lumina, one for ingress and one for egress of fluid. The system is self-contained, so that the fluid does not communicate in any way with the spinal fluid. A console device circulates cold fluid through the catheter. The catheter was tested in 5 adult sheep, with direct monitoring of core body temperature and spinal cord temperature in both active cooling and passive re-warming cycles. In testing in 4 sheep (five attempted implants, with one failure), the catheter worked without problem, producing effective cooling of the spinal cord, from a mean temperature of 36.8 degrees C (core temperature) to 30.5 degrees C (spinal temperature) ($p < 0.0001$). In no case did post-mortem examination or histology reveal any evidence of damage to the spinal cord from hypothermia. Temperature rose toward body temperature after cessation of active cooling. Effective topical cooling of the spinal cord can be achieved via a specially designed, self-contained cooling catheter placed

into the intra-thecal space. This catheter holds promise for spinal cord protection in aortic surgery. Also, this catheter may be useful as well in mitigating injury to the spinal cord in cases of traumatic spinal column injury.

Salzano *et al.* [25] tested in pigs the hypothesis that regional deep hypothermia of the spinal cord achieved by cerebrospinal fluid cooling will protect against ischemic injury during thoracic aortic cross-clamping. Eight control animals underwent aortic cross-clamping at the distal aortic arch and just above the diaphragm for 30 minutes. Eight experimental animals had placement of two subarachnoid perfusion catheters through laminectomies at T4 and the lower lumbar region. The subarachnoid space was perfused with normal saline solution at 6 degrees C delivered by gravity infusion, with infusion rates adjusted to maintain cord temperatures at less than 20 degrees C. After 30 minutes of aortic cross-clamping, the infusion was stopped and the cord allowed to warm to body temperature. Hind limb neurologic function was graded by Tarlov's scale. All of the animals in the control group had complete hind limb paraplegia (Tarlov grade 0) postoperatively. Seven of the 8 animals in the experimental group had preservation of hind limb motor function (Tarlov grade 2), and 1 animal had complete hind limb paraplegia (Tarlov grade 0) ($p = 0.002$, Fisher's exact test). It was concluded that regional deep hypothermia of the spinal cord in pigs does provide some protection from ischemic injury during thoracic aortic cross-clamping. Clinically this may be a useful adjunct for prevention of paraplegia during thoracic aortic operations.

It is reported that hypothermia has some protective effect against ischemia of the spinal cord during thoraco abdominal aneurysm repair. However, it has not been elucidated clinically whether regional spinal cord hypothermia by epidural perfusion cooling is effective and safe. Tabayashi *et al.* [26] assessed the effect and safety of perfusion cooling of the epidural space during most or all of descending thoracic or thoraco- abdominal aneurysm repair. From January 1998 to December 2007, a total of 102 patients with a mean age of 61 years underwent replacement of most or all of the descending thoracic aorta or thoraco-abdominal aorta with the aid of mild hypothermia via epidural perfusion cooling and cerebrospinal fluid (CSF) drainage. Risk factors for spinal cord injury and hospital death were analyzed using univariate and multivariate analyses. The actuarial survival rate was calculated by the Kaplan-Meier method. The mean lowest CSF temperature was 23.3 degrees C during epidural perfusion cooling. The mean temperature difference between the nasopharynx and CSF was 8.4 degrees C. The incidence of spinal cord injury was 3.9% (4/102), and that of hospital death was 5.9% (6/102). There was no significant risk factor associated with spinal cord injury. Type III aneurysm and postoperative cerebrovascular accident, respiratory failure, liver failure, and infection were predictors of hospital death. The actuarial survival rates at 3 and 5 years were 82.1% and 75.9%, respectively. Epidural perfusion cooling is a safe method to employ in clinical situations.

9. The Effect of Intrathecal Tetracaine on the Neurological Sequelae of Spinal Cord Ischemia and Reperfusion with Aortic Occlusion

Spinal cord ischemia and resultant paraplegia are devastating sequelae in up to 40% of patients undergoing repair of thoraco-abdominal aneurysms. Breckwoldt *et al.* [27] investigated the effect of intrathecal tetracaine on the neurological sequelae of spinal cord ischemia and reperfusion with aortic occlusion. Cocaine-derived anesthetics (lidocaine and its analogues) have been shown to decrease neuronal cell metabolism and also have specific neuronal membrane stabilizing effects. New Zealand white rabbits were anesthetized and spinal cord ischemia was then induced by infrarenal aortic occlusion. Animals were divided into six treatment groups. Tetracaine (groups 2 and 4) or normal saline solution (group 5) was administered intrathecally before aortic cross-clamping. Groups 1 and 3 functioned as controls. Group 6 animals received intravenous thiopental. Rabbits were classified as either neurologically normal or injured (paralyzed or paretic). Among controls, 25 minutes of aortic occlusion produced varied neurological sequelae (group 1, 3/6 injured, 50%) whereas 30 minutes resulted in more consistent injury (group 3, 5/6 injured, 83%). All rabbits that received intrathecal saline solution were paralyzed (group 5, 4/4 injured, 100%). Animals treated with intrathecal tetracaine and aortic occlusion of 30 minutes (group 4) showed significantly better preservation of neurological function (6/7 normal, 86%) than controls and saline-treated animals (groups 3 and 5). All animals treated with intrathecal tetracaine and aortic occlusion for 25 minutes (group 2) showed no signs of injury (5/5 normal, 100%), but this was not significant versus controls (group 1). Intravenous thiopental (group 6, 5/5 injured, 100%) had no beneficial effect. Intrathecal tetracaine significantly and dramatically abrogated the neurological injury secondary to spinal cord ischemia and reperfusion after aortic occlusion at 30 minutes in the rabbit model.

10. The Use of Prophylactic Hypothermia for Traumatic Brain Injury

During the past 9 years, considerable new evidence has

accumulated supporting the use of prophylactic hypothermia for traumatic brain injury (TBI). Studies can be divided into 2 broad categories: studies with protocols for cooling for a short, predetermined period (e.g., 24 - 48 h), and those that cool for longer periods and/or terminate based on the normalization of intracranial pressure (ICP). There have been no systematic reviews of hypothermia for TBI that include this recent new evidence.

This analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the QUOROM (quality of reporting of meta-analyses) statement. Fox *et al.* [28] developed a comprehensive search strategy to identify all randomized controlled trials (RCTs) comparing therapeutic hypothermia with standard management in TBI patients. They searched Embase, MEDLINE, Web of Science, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, ProceedingsFirst and PapersFirst. Additional relevant articles were identified by hand-searching conference proceedings and bibliographies. All stages of study identification and selection, quality assessment and analysis were conducted according to prospectively defined criteria. Study quality was determined by assessment of each study for the use of allocation concealment and outcome assessment blinding. Studies were divided into 2 a priori-defined subgroups for analysis based on cooling strategy: short term (≤48 h), and long term or goal-directed (>48 h and/or continued until normalization of ICP). Outcomes included mortality and good neurologic outcome (defined as Glasgow Outcome Scale score of 4 or 5). Pooling of primary outcomes was completed using relative risk (RR) and reported with 95% confidence intervals (CIs).

Of 1709 articles, 12 studies with 1327 participants were selected for quantitative analysis. Eight of these studies cooled according to a long-term or goal-directed strategy, and 4 used a short-term strategy. Summary results demonstrated lower mortality (RR 0.73, 95% CI 0.62 - 0.85) and more common good neurologic outcome (RR 1.52, 95% CI 1.28 - 1.80). When only short-term cooling studies were analyzed, neither mortality (RR 0.98, 95% CI 0.75 - 1.30) nor neurologic outcome (RR 1.31, 95% CI 0.94 - 1.83) were improved. In 8 studies of long-term or goal-directed cooling, mortality was reduced (RR 0.62, 95% CI 0.51 - 0.76) and good neurologic outcome was more common (RR 1.68, 95% CI 1.44 - 1.96).

The best available evidence to date supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (Glasgow Coma Scale score ≤ 8) to decrease mortality and improve rates of good neurologic recovery. This treatment should be commenced as soon as possible after injury (e.g., in the emergency department after computed tomography) regardless of initial ICP, or before ICP is measured. Most studies report using a temperature of 32 degrees - 34 degrees C. The maximal benefit occurred with a long-term or goal-directed cooling protocol, in which cooling was continued for at least 72 hours and/or until stable normalization of intracranial pressure for at least 24 hours was achieved.

Peterson *et al.* [29] conducted an updated meta-analysis of the effects of hypothermia therapy on mortality, favorable neurologic outcome, and associated adverse effects in adults with traumatic brain injury (TBI) for use by Brain Trauma Foundation (BTF)/American Association of Neurological Surgeons (AANS) task force to develop evidence-based treatment guidelines. The data sources relied on hand searches of four previous good-quality systematic reviews, which all conducted electronic searches of primarily MEDLINE (OVID), EMBASE, and Cochrane Library. An independent, supplemental electronic search of MEDLINE was undertaken as well (last searched June 2007). Only English-language publications of randomized controlled trials of therapeutic hypothermia in adults with TBI were selected for analysis. Two reviewers independently abstracted data on trial design, patient population, hypothermia and cointervention protocols, patient outcomes, and aspects of methodological quality. Pooled relative risks (RR) and associated 95% confidence intervals (CIs) were calculated for each outcome using random-effects models. In the current study, only 13 trials met eligibility criteria, with a total of 1339 randomized patients. Sensitivity analyses revealed that outcomes were influenced by variations in methodological quality. Consequently, main analyses were conducted based on eight trials that demonstrated the lowest potential for bias (n = 781). Reductions in risk of mortality were greatest (RR 0.51; 95% CI 0.33, 0.79) and favorable neurologic outcomes much more common (RR 1.91; 95% CI 1.28, 2.85) when hypothermia was maintained for more than 48 h. However, this evidence comes with the suggestion that the potential benefits of hypothermia may likely be offset by a significant increase in risk of pneumonia (RR 2.37; 95% CI 1.37, 4.10). In sum, the present study's updated meta-analysis supports previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Accordingly, the BTF/AANS guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI.

11. Lipid Neuroprotection

The harmony and function of the complex brain circuits

and synapses are sustained mainly by excitatory and inhibitory neurotransmission, neurotrophins, gene regulation, and factors, many of which are incompletely understood. A common feature of brain circuit components, such as dendrites, synaptic membranes, and other membranes of the nervous system, is that they are richly endowed in docosahexaenoic acid (DHA), the main member of the omega-3 essential fatty acid family. DHA is avidly retained and concentrated in the nervous system and known to play a role in neuroprotection, memory, and vision. Only recently has it become apparent why the surprisingly rapid increases in free (unesterified) DHA pool size take place at the onset of seizures or brain injury. This phenomenon began to be clarified by the discovery of neuroprotectin D1 (NPD1), the first-uncovered bioactive docosanoid formed from free DHA through 15-lipoxygenase-1 (15-LOX-1). NPD1 synthesis includes, as agonists, oxidative stress and neurotrophins. The evolving concept is that DHA-derived docosanoids set in motion endogenous signaling to sustain homeostatic synaptic and circuit integrity. NPD1 is anti-inflammatory, displays inflammatory resolving activities, and induces cell survival, which is in contrast to the pro-inflammatory actions of the many of omega-6 fatty acid family members. Bazan *et al.* [30] highlighted studies relevant to the ability of DHA to sustain neuronal function and protect synapses and circuits in the context of DHA signalolipidomics. DHA signalolipidomics comprises the integration of the cellular/tissue mechanism of DHA uptake, its distribution among cellular compartments, the organization and function of membrane domains containing DHA phospholipids, and the precise cellular and molecular events revealed by the uncovering of signaling pathways regulated by docosanoids endowed with prohomeostatic and cell survival bioactivity. Therefore, this approach offers emerging targets for prevention, pharmaceutical intervention, and clinical translation involving DHA-mediated signaling.

The significance of the selective enrichment in omega-3 essential fatty acids in photoreceptors and synaptic membranes of the nervous system has remained, until recently, incompletely understood. While studying mechanisms of cell survival in neural degeneration, Palacios-Pelaez *et al.* [31] discovered a docosanoid synthesized from unesterified docosahexaenoic acid (DHA) by a 15-lipoxygenase (15-LOX), which they called neuroprotectin D1 (NPD1; 10R,17S-dihydroxy-docosa-4Z,7Z, 11E,13E,15E,19Z hexaenoic acid). This lipid mediator is a docosanoid because it is derived from the 22 carbon (22C) precursor DHA, unlike eicosanoids, which are derived from the 20 carbon (20C) arachidonic acid (AA) family member of essential fatty acids. They discovered that NPD1 is promptly made in response to oxidative stress, as a response to brain ischemia-reperfusion, and in the presence of neurotrophins. NPD1 is neuroprotective in experimental brain damage, in oxidative-stressed retinal pigment epithelial (RPE) cells, and in human brain cells exposed to amyloid-beta (Abeta) peptides. They thus envision NPD1 as a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by imbalances in normal neural function. They provide here, in three sections, recent experimental examples that highlight the specificity and potency of NPD1 spanning beneficial bioactivity during initiation and early progression of neurodegeneration: 1) during retinal signal phototransduction, 2) during brain ischemia-reperfusion, and 3) in Alzheimer's disease (AD) and stressed human brain cell models of AD. From this experimental evidence, they conclude that DHA-derived NPD1 regulation targets upstream events of brain cell apoptosis, as well as neuro-inflammatory signaling, promoting and maintaining cellular homeostasis, and restoring neural and retinal cell integrity.

Deficiency in docosahexaenoic acid (DHA) is associated with impaired visual and neurological development, cognitive decline, macular degeneration, and other neurodegenerative diseases. DHA is concentrated in phospholipids of the brain and retina, with photoreceptor cells having the highest DHA content of all cell membranes. The discovery that neuroprotectin D1 (NPD1; 10R, 17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) is a bioactive mediator of DHA sheds light on the biological importance of this fatty acid. In oxidative stress-challenged human retinal pigment epithelial (RPE) cells, human brain cells, or brain ischemia-reperfusion, NPD1 synthesis is enhanced as a response for sustaining homeostasis. Thus, neurotrophins, Abeta peptide (Abeta42), calcium ionophore A23187, interleukin-1beta (IL-1beta), or DHA supply enhances NPD1 synthesis. NPD1, in turn, upregulates the antiapoptotic proteins of the Bcl-2 family and decreases the expression of proapoptotic Bcl-2 family members. In human neural cells, DHA attenuates Abeta42 secretion, resulting in concomitant formation of NPD1. NPD1 repressed Abeta42-triggered activation of proinflammatory genes and upregulated the antiapoptotic genes encoding Bcl-2, Bcl-xl, and Bfl-1(A1) in human brain cells in culture. Overall, NPD1 signaling regulates brain and retinal cell survival via the induction of antiapoptotic and neuroprotective gene-expression programs that suppress Abeta42-induced neurotoxicity and other forms of cell injury. These in turn support homeostasis during brain and retinal aging, counteract inflammatory signaling, and downregulate events that support the initiation and progression of neurodegenerative disease [32].

Maciá-Botejara *et al.* [33] studied the changes occur-

ring in brain lipid composition after the administration of total parenteral nutrition (TPN) by comparing two lipid emulsions, one with long-chain triacylglycerols (LCT) and the other with long-chain and medium-chain triacylglycerols (MCT/LCT 50%/50%).

They used 21 young New Zealand rabbits divided into three groups of seven animals each. Two groups were subjected to TPN for 7 d, with each group receiving using one of two different lipid emulsions: Intralipid 20% (group LCT) and Lipofundin MCT/LCT 20% (group MCT/LCT). The third control group received an oral diet and underwent the same surgical procedure with the administration of intravenous saline solution. The energy administered in the TPN formulas was non-protein 100 $kcal \cdot kg^{-1} \cdot d^{-1}$, with 40% corresponding to fats.

There were modest increases in plasma cholesterol and triacylglycerols. In the brain tissue, there was a decrease of phosphatidylcholine in animals with TPN, which was greater in group LCT. There were no significant differences in the overall percentage distribution of brain fatty acids among the groups.

The lipid emulsions administered in TPN, especially those prepared exclusively with LCT, cause changes in the brain lipid polar fractions of young rabbits.

12. Lipid Resuscitation Therapy

On 1998 it was first showed that intravenous intralipid could prevent or improve resuscitation from cardiovascular collapse by severe bupivacaine overdose in rats.

Since then published examples now include toxicities related to verapamil, diltiazem, amlodipine, quetiapine and sertraline, haloperidol, lamotrigine, olanzapine, propranolol, atenolol, nevibolol, doxepin, dosulepin, imipramine, amitriptyline, glyosphate herbicide, flecainide, venlafaxine, moxidectin, and others.

Lipid resuscitation therapy using intravenous lipid emulsion (IVLE) for drug overdoses has gained widespread use. However, there is little information regarding its adverse effects.

Grunbaum *et al.* [34] performed lipemic interference studies on typical automated platforms to investigate the potential of lipid resuscitation therapy to interfere with the reliability and turnaround time of analytes that would be of interest in acute intoxications. They also tested methods to minimize interferences.

Serum pools were supplemented with increasing concentrations of Intralipid-20%(®) (0% - 30%). Analyses were performed on Beckman-Coulter DXC800 and DXI and Roche Modular-P. Analytes demonstrating significant interference were re-measured after centrifugation (14,000 × g for 10 minutes).

Triglyceride and glycerol-blanked triglyceride concentrations were similar in IVLE-free samples. However, with addition of IVLE, concentrations were markedly different (139 vs. 76 mmol/L). There was no appreciable interference on the troponin-I, sodium, potassium, chloride, calcium, bicarbonate or urea assays. Albumin and magnesium assays demonstrated significant interference. Amylase, lipase, phosphate, creatinine, total protein, ALT, CK and bilirubin became unmeasurable in IVLE-supplemented samples. Whereas glucose measurement by potentiometry was free of interference, colorimetric methodology was error prone. Centrifugation removed > 90% of glycerol-blanked triglyceride (max = 5.8 mmol/L), dramatically reducing lipid interferences.

IVLE results in appreciable analytical interferences at concentrations demonstrated in lipid resuscitation therapy. Of particular concern is the marked interference on glucose and magnesium, which may result in unsuccessful and potentially harmful interventions. Major implications for patient care include reporting of incorrect results and delays in the reporting of time-sensitive results. Whenever possible, blood samples should be collected prior to initiating lipid therapy. Interferences can be minimized by brief centrifugation at relatively low speeds on equipment readily available in most core labs.

Li *et al.* [35] have recently shown that post-ischemic administration of intralipid protects the heart against ischemia-reperfusion injury. They compared the cardioprotective effects of intralipid with cyclosporine-A, a potent inhibitor of the mitochondrial permeability transition pore opening.

In vivo rat hearts or isolated Langendorff-perfused mouse hearts were subjected to ischemia followed by reperfusion with intralipid (0.5%, 1% and 2% *ex vivo*, and 20% *in vivo*), cyclosporine-A (0.2 μM, 0.8 μM, and 1.5 μM *ex vivo* and 10 mg/kg *in vivo*), or vehicle. The hemodynamic function, infarct size, calcium retention capacity, mitochondrial superoxide production, and phosphorylation levels of protein kinase B (Akt)/glycolgen synthase kinase-3β (GSK-3β) were measured. The values are mean ± SEM.

Administration of intralipid at reperfusion significantly reduced myocardial infarct size compared with cyclosporine-A *in vivo* (infarct size/area at risk)%: 22.9% ± 2.5% vs. 35.2% ± 3.5%; p = 0.030, n = 7/group). Post-ischemic administration of intralipid at its optimal dose (1%) was more effective than cyclosporine-A (0.8 μM) in protecting the *ex vivo* heart against ischemia-reperfusion injury, as the rate pressure product at the end of reperfusion was significantly higher (mmHg·beats/min: 12,740 ± 675 [n = 7] vs. 9203 ± 10,781 [n = 5], p = 0.024), and the infarct size was markedly smaller (17.3 ± 2.9 [n = 7] vs. 29.2 ± 2.7 [n = 5], p = 0.014). Intralipid was as efficient as cyclosporine-A in inhibiting the mitochondrial permeability transition pore opening (calcium retention ca-

pacity = 280 ± 8.2 vs. 260.3 ± 2.9 nmol/mg mitochondria protein in cyclosporine-A, p = 0.454, n = 6) and in reducing cardiac mitochondrial superoxide production. Unlike intralipid, which increased phosphorylation of Akt (6-fold) and GSK-3β (5-fold), cyclosporine-A had no effect on the activation of these prosurvival kinases.

Although intralipid inhibits the opening of the mitochondrial permeability transition pore as efficiently as cyclosporine-A, intralipid is more effective in reducing the infarct size and improving the cardiac functional recovery.

13. Pretreatment or Resuscitation with a Lipid Infusion

INTRALIPID® 10% (10% i.v fat emulsion) (A 10% INTRAVENOUS FAT EMULSION) IS A STERILE, NON-PYROGENIC FAT EMULSION PREPARED FOR INTRAVENOUS ADMINISTRATION AS A SOURCE OF CALORIES AND ESSENTIAL FATTY ACIDS. IT IS MADE UP OF 10% SOYBEAN OIL, 1.2% EGG YOLK PHOSPHOLIPIDS, 2.25% GLYCERIN, AND WATER FOR INJECTION. IN ADDITION, SODIUM HYDROXIDE HAS BEEN ADDED TO ADJUST THE PH SO THAT THE FINAL PRODUCT PH IS 8. PH RANGE IS 6 TO 8.9.

THE SOYBEAN OIL IS A REFINED NATURAL PRODUCT CONSISTING OF A MIXTURE OF NEUTRAL TRIGLYCERIDES OF PREDOMINANTLY UNSATURATED FATTY ACIDS. THE MAJOR COMPONENT FATTY ACIDS ARE LINOLEIC (44% - 62%), OLEIC (19% - 30%), PALMITIC (7% - 14%), LINOLENIC (4% - 11%) AND STEARIC (1.4% - 5.5%).

PURIFIED EGG PHOSPHATIDES ARE A MIXTURE OF NATURALLY OCCURRING PHOSPHOLIPIDS WHICH ARE ISOLATED FROM THE EGG YOLK.

INTRALIPID® 10% (10% i.v fat emulsion) (A 10% INTRAVENOUS FAT EMULSION) HAS AN OSMOLALITY OF APPROXIMATELY 300 MOSMOL/KG WATER (WHICH REPRESENTS 260 MOS-MOL/LITER OF EMULSION) AND CONTAINS EMULSIFIED FAT PARTICLES OF APPROXIMATELY 0.5 MICRON SIZE.

THE TOTAL CALORIC VALUE, INCLUDING FAT, PHOSPHOLIPID AND GLYCERIN, IS 1.1 KCAL PER ML OF INTRALIPID 10% (10% i.v fat emulsion). THE PHOSPHOLIPIDS PRESENT CONTRIBUTE 47 MILLIGRAMS OR APPROXIMATELY 1.5 MMOL OF PHOSPHORUS PER 100 ML, OF THE EMULSION.

Weinberg *et al.* [36] first showed in 1998 that an infusion of a soybean oil emulsion normally used as a total parenteral nutrition solution could prevent (by pretreatment) or improve resuscitation from cardiovascular collapse caused by severe bupivacaine overdose in the intact, anesthetized rat. Subsequent studies from the same laboratory confirmed these findings in isolated rat heart [37] and anesthetized dog [38].

Under the latter experimental model, return of spontaneous circulation after a bupivacaine challenge occurred in all animals receiving lipid, but in none of the saline controls [38]. This study was accompanied by an editorial asking whether lipid might be the long-sought "silver bullet" for local anesthetic systemic toxicity (LAST). Since then, the effectiveness of lipid emulsion infusion in reversing LAST has been confirmed in other laboratories and by systematic analysis [39] and in the clinical setting as well.

Lipid infusion is useful in reversing cardiac toxicity of local anesthetics, and recent reports indicate it may be useful in resuscitation from toxicity induced by a variety of other drugs. While the mechanism behind the utility of lipid rescue remains to be fully elucidated, the predominant effect appears to be creation of a "lipid sink".

French D *et al.* [40] tried to determine whether the extraction of drugs by lipid, and hence the clinical efficacy of lipid rescue in toxicological emergencies can be predicted by specific drug properties.

Each drug investigated was added individually to human drug-free serum. Intralipid® was added to this drug-containing serum, shaken and then incubated at 37˚C. The lipid was removed by ultracentrifugation and the concentration of drug remaining in the serum was measured by high-pressure liquid chromatography.

In this in vitro model, the ability of lipid emulsion to bind a drug was largely dependent upon the drug's lipid partition constant. Additionally, using a multiple linear regression model, the prediction of binding could be improved by combining the lipid partition constant with the volume of distribution together accounting for approximately 88% of the variation in the decrease in serum drug concentration with the administration of lipid emulsion.

The lipid partition constant and volume of distribution can likely be used to predict the efficacy of lipid infusion in reversing the cardiac toxicity induced by anesthetics or other medications.

Local anaesthetics may induce cardiac arrest, usually because of rapid absorption from the site of injection or because of an intended intravascular injection. Early central nervous system symptoms usually precede seizures. Cardiac arrhythmias follow the CNS signs. These arrhythmias often resolve with the i.v. bolus injection of 100 to 150 mL of a lipid emulsion (20% Intralipid(®)). Although long acting local anaesthetics (bupivacaine, ropivacaine, levobupivacaine) are predominantly involved in this cardiac toxicity, lidocaine may also induce

cardiac arrhythmias and clinician must be aware of this risk. In case of cardiac arrest, resuscitation manoeuvres are of major importance. They need to be performed immediately and the efficacy of the lipid rescue requires a correct coronary flow to be efficacious. Finally, prevention is the key of a safe injection. It is important to control the dose, to inject slowly, without any excessive pressure and to verify that no blood reflux occurs [41].

14. Intralipid Reversing other Drugs Toxicity

These publications, along with other animal studies, opened the door to more widespread use of lipid emulsion for emergency treatment of toxicities caused by a range of lipophilic drugs. Notably, published examples now include toxicities related to verapamil, diltiazem, amlodipine, quetiapine and sertraline, haloperidol, lamotrigine, olanzapine, propranolol, atenolol, nevibolol, doxepin, dosulepin, imipramine, amitriptyline, glyosphate herbicide, flecainide, venlafaxine, moxidectin, and others.

Tricyclic antidepressant (TCA) toxicity results predominantly from myocardial sodium-channel blockade. Subsequent ventricular dysrhythmias, myocardial depression, and hypotension cause cardiovascular collapse. Animal studies have demonstrated the effectiveness of intravenous lipid-emulsion in treating TCA cardiotoxicity.

Blaber MS *et al.* [42] report a case of dothiepin (tricyclic antidepressant) overdose causing refractory cardiovascular collapse, which seemed to be successfully reversed with lipid-emulsion therapy (Intralipid®; Fresenius, Cheshire, UK).

Lipid emulsions are a potentially novel therapy for reversing cardiotoxicity seen in TCA overdose. Research is required into the role of lipid emulsion in the management of poisoning by oral lipophilic agents.

15. The Lipid Sink Effect

Papadopoulou A *et al.* [43] hypothesized that by substituting a dye surrogate in place of local anesthetic, they could visually demonstrate dye sequestration by lipid emulsion that would be dependent on both dye lipophilicity and the amount of lipid emulsion used.

They selected 2 lipophilic dyes, acid blue 25 and Victoria blue, with log P values comparable to lidocaine and bupivacaine, respectively. Each dye solution was mixed with combinations of lipid emulsion and water to emulate “lipid rescue” treatment at dye concentrations equivalent to fatal, cardiotoxic, and neurotoxic local anesthetic plasma concentrations. The lipid emulsion volumes added to each dye solution emulated equivalent intravenous doses of 100, 500, and 900 mL of 20% Intralipid in a 75-kg adult. After mixing, the samples were separated into a lipid-rich supernatant and a lipid-poor subnatant by heparin flocculation. The subnatants were isolated, and their colors compared against a graduated dye concentration scale.

Lipid emulsion addition resulted in significant dye acquisition by the lipid compartment accompanied by a reduction in the color intensity of the aqueous phase that could be readily observed. The greatest amount of sequestration occurred with the dye possessing the higher log P value and the greatest amount of lipid emulsion.

This study provides a visual demonstration of the lipid sink effect. It supports the theory that lipid emulsion may reduce the amount of free drug present in plasma from concentrations associated with an invariably fatal outcome to those that are potentially survivable.

Local anesthetic (LA) intoxication with cardiovascular arrest is a potential fatal complication of regional anesthesia. Lipid resuscitation has been recommended for the treatment of LA-induced cardiac arrest. Aim of the study [34] was to compare four different rescue regimens using epinephrine and/or lipid emulsion and vasopressin to treat cardiac arrest caused by bupivacaine intoxication.

Twenty-eight piglets were randomized into four groups (4 × 7), anesthetized with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via central venous catheter at a rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ until circulatory arrest. Bupivacaine infusion and sevoflurane were then stopped, chest compression was started, and the pigs were ventilated with 100% oxygen. After 1 min, epinephrine 10 $\mu g \cdot kg^{-1}$ (group 1), Intralipid(®) 20% 4 $ml \cdot kg^{-1}$ (group 2), epinephrine 10 $\mu g \cdot kg^{-1}$ + Intralipid(®) 4 $ml \cdot kg^{-1}$ (group 3) or 2 IU vasopressin + Intralipid(®) 4 $ml \cdot kg^{-1}$ (group 4) were administered. Secondary epinephrine doses were given after 5 min if required.

Survival was 71%, 29%, 86%, and 57% in groups 1, 2, 3, and 4. Return of spontaneous circulation was regained only by initial administration of epinephrine alone or in combination with Intralipid(®). Piglets receiving the combination therapy survived without further epinephrine support. In contrast, in groups 2 and 4, return of spontaneous circulation was only achieved after secondary epinephrine rescue.

In cardiac arrest caused by bupivacaine intoxication, first-line rescue with epinephrine and epinephrine + Intralipid(®) was more effective with regard to survival than Intralipid(®) alone and vasopressin + Intralipid(®) in this pig model [44].

Local anesthetic (LA) intoxication with severe hemodynamic compromise is a potential catastrophic event. Lipid resuscitation has been recommended for the treat-

ment of LA-induced cardiac arrest. However, there are no data about effectiveness of Intralipid for the treatment of severe cardiovascular compromise prior to cardiac arrest. Aim of this study was to compare effectiveness of epinephrine and Intralipid for the treatment of severe Hemodynamic compromise owing to bupivacaine intoxication, anesthetized Piglets were with sevoflurane, intubated, and ventilated. Bupivacaine was infused with a syringe driver via a central venous catheter at a rate of 1 $mg \cdot kg^{-1} \cdot min^{-1}$ until invasively measured mean arterial pressure (MAP) dropped to 50% of the initial value. Bupivacaine infusion was then stopped, and epinephrine 3 $\mu g \cdot kg^{-1}$ (group 1), Intralipid(®) 20% 2 $ml \cdot kg^{-1}$ (group 2), or Intralipid 20% 4 $ml \cdot kg^{-1}$ (group 3) was immediately administered. Twenty-one piglets (3 × 7), were recorded. All animals in group 1 (100%) but only four of seven (57%) piglets in group 2 and group 3, respectively, survived. Normalization of hemodynamic parameters (HR, MAP) and ET(CO_2) was fastest in group 1 with all piglets achieving HR and MAP values. hemodynamic compromise owing to bupivacaine intoxication in piglets, first-line rescue with epinephrine was more effective than Intralipid with regard to survival as well as normalization of hemodynamic parameters and ET(CO_2) [45].

Intravenous lipid emulsion (ILE) has been proposed as a rescue therapy for severe local anesthetic drugs toxicity, but experience is limited with other lipophilic drugs. An 18-year-old healthy woman was admitted 8 h after the voluntary ingestion of sustained-release diltiazem (3600 mg), with severe hypotension refractory to fluid therapy, calcium salts, and high-dose norepinephrine (6.66 μg/kg/min). Hyperinsulinemic euglycemia therapy was initiated and shortly after was followed by a protocol of ILE (intralipid 20%, 1.5 ml/kg as bolus, followed by 0.25 ml/kg over 1h). The main finding attributed to ILE was an apparent rapid decrease in insulin resistance, despite a prolonged serum diltiazem elimination half-life. Diltiazem is a lipophilic cardiotoxic drug, which could be sequestered in an expanded plasma lipid phase. The mechanism of action of ILE is not known, including its role in insulin resistance and myocardial metabolism in calcium-channel blocker poisoning [46].

16. Guidelines for the Management of Local Anaesthetic Toxicity

There is increasing evidence for the use of Intralipid in the management of acute local anaesthetic toxicity. This is supported by the recent Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines for the management of local anaesthetic toxicity. Acute hospitals in England and Wales were surveyed to determine the proportion that currently stocked Intralipid, the locations of stocks within the hospital, guidelines related to its use and previous use in the last 12 months. The majority of hospitals surveyed stocked Intralipid in multiple locations, although not in all areas using high volumes of local anaesthetics. Guidelines were typically in place, although these were often local rather than those from the AAGBI. Use in the last 12 months was uncommon, but typically information was not available on indications for its use. More systematic data collection is required on the safety and efficacy of Intralipid in the management of acute drug toxicity [47].

Intralipid therapy has been used successfully as "rescue therapy" in several cases of overdose. West PL *et al.* [48] present a case of iatrogenic lipid emulsion overdose because of a dosing error:

"A 71-year-old female overdosed on 27 tablets of 5 mg amlodipine. Although initially stable in the Emergency Department, she became hypotensive, oliguric, and respiratory failure developed despite medical therapy. The primary treating team felt that meaningful recovery was unlikely to occur without rapid improvement in clinical status, and 12.5 h after presentation, intralipid rescue therapy was initiated. A protocol for intralipid specifying a maximum infusion of 400 mL of 20% lipid emulsion was faxed, but the infusion was continued until 2 L of lipid emulsion was infused. There were no detectable adverse hemodynamic effects of the intralipid infusion. After this time, laboratory values were difficult to obtain. Three hours after the infusion, a metabolic panel was obtained from ultracentrifuged blood showing hyponatremia. A white blood cell (WBC) was obtained from a complete blood count (CBC) performed 22 h after the infusion, hemoglobin and hematocrit could not be obtained from this blood. A platelet count was obtained by smear estimate. Hematocrits were obtained from centrifuged blood and appeared elevated. No oxygenation could be obtained on blood gas. The patient's family chose to withdraw care on hospital day 2 and no further laboratory draws were obtained. Amlodipine was 1500 ng/mL (ref. 3 - 11 ng/mL)."

17. Lipid Emulsion Overdose

Lipid emulsion overdose caused no detectable acute adverse hemodynamic effects. The following laboratory values were unobtainable immediately after infusion: white blood cell count, hemoglobin, hematocrit, platelet count, and a metabolic panel of serum electrolytes. Ultracentrifugation of blood allowed for detection of a metabolic panel 3 h after the infusion. Centrifuged hematocrits appeared to be higher than expected.

Lipid infusion reverses systemic local anesthetic toxicity. The acceptable upper limit for lipid administration is unknown and has direct bearing on clinical management. Hiller DB *et al.* [49] hypothesize that high volumes of

lipid could have undesirable effects and sought to identify the dose required to kill 50% of the animals (LD(50)) of large volume lipid administration.

Intravenous lines and electrocardiogram electrodes were placed in anesthetized, male Sprague-Dawley rats. Twenty percent lipid emulsion (20, 40, 60, or 80 mL/kg) or saline (60 or 80 mL/kg), were administered over 30 mins; lipid dosing was assigned by the Dixon "up-and-down" method. Rats were recovered and observed for 48 hrs then euthanized for histologic analysis of major organs. Three additional rats were administered 60 mL/kg lipid emulsion and euthanized at 1, 4, and 24 hrs to identify progression of organ damage.

The maximum likelihood estimate for LD(50) was 67.72 (SE, 10.69) mL/kg. Triglycerides were elevated immediately after infusion but returned to baseline by 48 hrs when laboratory abnormalities included elevated amylase, aspartate aminotransferase, and serum urea nitrogen for all lipid doses. Histologic diagnosis of myocardium, brain, pancreas, and kidneys was normal at all doses. Microscopic abnormalities in lung and liver were observed at 60 and 80 mL/kg; histopathology in the lung and liver was worse at 1 hr than at 4 and 24 hrs.

The LD(50) of rapid, high volume lipid infusion is an order of magnitude greater than doses typically used for lipid rescue in humans and supports the safety of lipid infusion at currently recommended doses for toxin-induced cardiac arrest. Lung and liver histopathology was observed at the highest infused volumes.

18. Intralipid Rescue: 1966-2009

Cave G and Harvey M [50] evaluate the efficacy of lipid emulsion as antidotal therapy outside the accepted setting of local anesthetic toxicity.

Literature was accessed through PubMed, OVID (1966-February 2009), and EMBASE (1947-February 2009) using the search terms "intravenous" AND ["fat emulsion" OR "lipid emulsion" OR "Intralipid"] AND ["toxicity" OR "resuscitation" OR "rescue" OR "arrest" OR "antidote"]. Additional author and conference publication searches were undertaken. Publications describing the use of lipid emulsion as antidotal treatment in animals or humans were included.

Fourteen animal studies, one human study, and four case reports were identified. In animal models, intravenous lipid emulsion (ILE) has resulted in amelioration of toxicity associated with cyclic antidepressants, verapamil, propranolol, and thiopentone. Administration in human cases has resulted in successful resuscitation from combined bupropion/lamotrigine-induced cardiac arrest, reversal of sertraline/quetiapine-induced coma, and amelioration of verapamil- and beta blocker-induced shock.

Management of overdose with highly lipophilic cardiotoxic medications should proceed in accord with established antidotal guidelines and early poisons center consultation. Data from animal experiments and human cases are limited, but suggestive that ILE may be helpful in potentially lethal cardiotoxicity or developed cardiac arrest attributable to such agents. Use of lipid emulsion as antidote remains a nascent field warranting further preclinical study and systematic reporting of human cases of use.

Previous investigators have demonstrated amelioration of lipid-soluble drug toxidromes with infusion of lipid emulsions. Clomipramine is a lipid-soluble tricyclic antidepressant with significant cardiovascular depressant activity in human overdose. Harvey M and Cave G [51] compare resuscitation with Intralipid versus sodium bicarbonate in a rabbit model of clomipramine toxicity.

Thirty sedated and mechanically ventilated New Zealand White rabbits were infused with clomipramine at 320 mg/kg per hour. At target mean arterial pressure of 50% initial mean arterial pressure, animals were rescued with 0.9% NaCl 12 mL/kg, 8.4% sodium bicarbonate 3 mL/kg, or 20% Intralipid 12 mL/kg. Pulse rate, mean arterial pressure, and QRS duration were sampled at 2.5-minute intervals to 15 minutes. In the second phase of the experiment, 8 sedated and mechanically ventilated rabbits were infused with clomipramine at 240 mg/kg per hour to a mean arterial pressure of 25 mm Hg. Animals received either 2 mL/kg 8.4% sodium bicarbonate or 8 mL/kg 20% Intralipid as rescue therapy. External cardiac compression and intravenous adrenaline were administered in the event of cardiovascular collapse.

Mean difference in mean arterial pressure between Intralipid- and saline solution-treated groups was 21.1 mm Hg (95% confidence interval [CI] 13.5 to 28.7 mm Hg) and 19.5 mm Hg (95% CI 10.5 to 28.9 mm Hg) at 5 and 15 minutes, respectively. Mean difference in mean arterial pressure between Intralipid- and bicarbonate-treated groups was 19.4 mm Hg (95% CI 18.8 to 27.0 mm Hg) and 11.5 mm Hg (95% CI 2.5 to 20.5 mm Hg) at 5 and 15 minutes. The rate of change in mean arterial pressure was greatest in the Intralipid-treated group at 3 minutes (6.2 mm Hg/min [95% CI 3.8 to 8.6 mm Hg/min]). In the second phase of the experiment spontaneous circulation was maintained in all Intralipid-treated rabbits (n = 4). All animals in the bicarbonate-treated group developed pulseless electrical activity and proved refractory to resuscitation at 10 minutes (n = 4, p = 0.023).

In this rabbit model, Intralipid infusion resulted in more rapid and complete reversal of clomipramine-induced hypotension compared with sodium bicarbonate. Additionally, Intralipid infusion prevented cardiovascular collapse in a model of severe clomipramine toxicity.

19. Intralipid Prevents and Rescues Fatal Pulmonary Arterial Hypertension and Right Ventricular Failure and Enhances the Inflammatory Response to Endotoxin

Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling leading to right ventricular (RV) hypertrophy and failure. Intralipid (ILP), a source of parenteral nutrition for patients, contains γ-linolenic acid and soy-derived phytoestrogens that are protective for lungs and heart. Umar S. *et al.* [52] investigated the therapeutic potential of ILP in preventing and rescuing monocrotaline-induced PAH and RV dysfunction. PAH was induced in male rats with monocrotaline (60 mg/kg). Rats then received daily ILP (1 mL of 20% ILP per day IP) from day 1 to day 30 for prevention protocol or from day 21 to day 30 for rescue protocol. Other monocrotaline-injected rats were left untreated to develop severe PAH by day 21 or RV failure by approximately day 30. Saline or ILP-treated rats served as controls. Significant increase in RV pressure and decrease in RV ejection fraction in the RV failure group resulted in high mortality. Therapy with ILP resulted in 100% survival and prevented PAH-induced RV failure by preserving RV pressure and RV ejection fraction and preventing RV hypertrophy and lung remodeling. In preexisting severe PAH, ILP attenuated most lung and RV abnormalities. The beneficial effects of ILP in PAH seem to result from the interplay of various factors, among which preservation and/or stimulation of angiogenesis, suppression and/or reversal of inflammation, fibrosis and hypertrophy, in both lung and RV, appear to be major contributors. In conclusion, ILP not only prevents the development of PAH and RV failure but also rescues preexisting severe PAH [52].

Novel anti-inflammatory effects of insulin have recently been described, and insulin therapy to maintain euglycemia suppresses the plasma levels of free fatty acids (FFA) and increases the survival of critically ill patients. Krogh-Madsen *et al.* [53] aimed to explore the effect of short-term high levels of plasma FFA on the inflammatory response to a low dose of endotoxin. Fourteen healthy male volunteers underwent the following two trials in a randomized crossover design: 1) continuous infusion of 20% Intralipid [0.7 $ml \cdot kg^{-1} \cdot h^{-1}$ (1.54 g/kg)] for 11 h, and 2) infusion of isotonic saline for 11 h (control). In each trial, heparin was given to activate lipoprotein lipase, and an intravenous bolus of endotoxin (0.1 ng/kg) was given after 6 h of Intralipid/saline infusion. Blood samples and muscle and fat biopsies were obtained before the Intralipid/saline infusion and before as well as after infusion of an endotoxin bolus. Plasma levels of FFA, triglycerides, and glycerol were markedly increased during the Intralipid infusion. Endotoxin exposure induced an increase in plasma levels of TNF-alpha, IL-6, and neutrophils and further stimulated gene expression of TNF-alpha and IL-6 in both skeletal muscle and adipose tissue. The systemic inflammatory response to endotoxin was significantly pronounced during Intralipid infusion. Short-term hyperlipidemia enhances the inflammatory response to endotoxin, and skeletal muscle and adipose tissue are capable of producing essential inflammatory mediators after endotoxin stimulation.

20. Is Intralipid Approved by the FDA for Local Anesthesia-Induced Cardiovascular Collapse or Resuscitation?

As with any FDA-labeled medication, the individual Intralipid products carry with them a set of contraindications to use and adverse effects. However, the extent to which these apply in the setting of Local Anesthesia-induced cardiovascular collapse or resuscitation, for which Intralipid is not FDA-approved, remains to be defined. The general contraindication to Intralipid use is the presence of disorders of fat metabolism. Other contraindications not published in the product's package insert include egg allergy and acute myocardial infarction. The use of Intralipid is cautioned in patients with anemia, severe liver disease, coagulopathies, pulmonary disease, and in patients at risk for fat embolism. The most common adverse effects from general Intralipid use are those related to contamination of the administration site and irritation of the veins likely due to other solutions co-infused with Intralipid.

Early or immediate adverse effects of Intralipid include allergic reactions, headache, somnolence, dizziness, diaphoresis, dyspnea, nausea/vomiting, hyperthermia, and hypercoagulability. More delayed adverse effects of Intralipid include thrombocytopenia, jaundice, overloading syndrome, increased liver function tests, leucopenia, hepatomegaly, and splenomegaly; pancreatitis has rarely been associated with Intralipid use. Those adverse effects that may be dose- or rate-related include pulmonary embolus or fat embolus, and pulmonary vasoconstriction may result from bolus administration of Intralipid. There were no adverse effects reported with Intralipid use in the four human case reports after Local Anesthesia -induced cardiovascular collapse, although further investigation is warranted [54].

21. Conclusions

A new multimodal proposal for spinal cord and brain treatment and protection due to injuries and diseases has been described:

The epidural catheter is used for cooled saline injection and infusion.

The spinal catheter is used for Intralipid spinal injections and CSF aspiration.

The proposal is based on the current studies on spinal cord cooling and CSF aspiration as well as on the Intralipid resuscitation properties and lipid brain protection.

A study is needed to evaluate the clinical value of this multimodal spinal and brain treatment and disease prevention.

REFERENCES

[1] Y. M. Wang, "Compositions and Treatment Method for Brain and Spinal Cord Injuries," Patent No. US 6683066 B2, 2004.

[2] S. W. Hoffman, A. L. Kellermann, D. G. Stein, D. W. Wright and D. W. Lowery-North, "Dosage Regimen for the Treatment of a Traumatic Brain Injury with Progesterone," Patent No. EP 1868614 A2, 2007.

[3] M. Eisenbach-Schwartz, E. Yoles and E. Hauben, "Use of Poly-Glu, Tyr for Neuroprotection Therapy of the Cns or Pns," Patent No. EP 1406650 B1, 2008.

[4] J. Whyte and M. Rosenthal, "Rehabilitation of the Patient with Traumatic Brain Injury," In: J. A. DeLisa, Ed., *Rehabilitation Medicine*: *Principles and Practice*, 2nd Edition, Lippincott, Philadelphia, 1993, pp. 825-860.

[5] R. F. Frankowski, J. F. Annegers and S. Whitman, "The Descriptive Epidemiology of Head Trauma in the United States," In: D. P. Becker and J. T. Povlishock, Eds., *Central Nervous System Research Status Report*, NINCDS; Bethesda, 1985, pp. 33-43.

[6] M. E. Sandel and M. Finch, "The Case for Comprehensive Residency Training in Traumatic Brain Injury: A Commentary," *American Journal of Physical Medicine & Rehabilitation*, Vol. 72, No. 5, 1993, pp. 325-326. http://dx.doi.org/10.1097/00002060-199310000-00013

[7] B. Jennett and M. Bond, "Assessment of Outcome in Severe Brain Damage," *The Lancet*, Vol. 305, No. 7905, 1975, pp. 480-484. http://dx.doi.org/10.1016/S0140-6736(75)92830-5

[8] J. F. Kraus and D. L. McArthur, "Epidemiologic Aspects of Brain Injury," *Neurologic Clinics*, Vol. 14, No. 2, 1996, pp. 435-450. http://dx.doi.org/10.1016/S0733-8619(05)70266-8

[9] W. Max, E. J. Mackenzie and D. P. Rice, "Head Injuries: Costs and Consequences," *Journal of Head Trauma Rehabilitation*, Vol. 6, No. 2, 1991, pp. 76-91. http://dx.doi.org/10.1097/00001199-199106000-00010

[10] W. R. McMordie and S. L. Barker, "The Financial Trauma of Head Injury," *Brain Injury*, Vol. 2, No. 4, 1988, pp. 357-364. http://dx.doi.org/10.3109/02699058809150908

[11] M. R. Bullock, B. G. Lyeth and J. P. Muizelaar, "Current Status of Neuroprotection Trials for Traumatic Brain Injury: Lessons from Animal Models and Clinical Studies," *Neurosurgery*, Vol. 45, No. 2, 1999, pp. 207-217. http://dx.doi.org/10.1097/00006123-199908000-00001

[12] L. D. Lehmkuhl, K. M. Hall, N. Mann and W. A. Gordon, "Factors That Influence Costs and Length of Stay of Persons with Traumatic Brain Injury in Acute Care and Inpatient Rehabilitation," *Journal of Head Trauma Rehabilitation*, Vol. 8, No. 2, 1993, pp. 88-100. http://dx.doi.org/10.1097/00001199-199308020-00010

[13] M. Bennett, D. P. OBrien, J. P. Phillips and M. A. Farrell, "Clinicopathologic Observations in 100 Consecutive Patients with Fatal Head Injury Admitted to a Neurosurgical Unit," *Irish Medical Journal*, Vol. 88, No. 2, 1995, pp. 60-62.

[14] J. M. Meythaler and J. Peduzzi, "Method of Treating Traumatic Brain and Spinal Cord Injuries and Other Neurogenic Conditions Using Non-Steroidal Anti-Inflammatory Drugs and Naturally Occurring Conotoxins," Patent No. EP 1210100 A4, 2004.

[15] F. Odaibo, C. A. Fajardo and C. Cronin, "Recovery of Intralipid from Lumbar Puncture after Migration of Saphenous Vein Catheter," *Archives of Disease in Childhood*, Vol. 67, No. 10, 1992, pp. 1201-1203.

[16] Y. Koga, N. Iwatsuki, M. Takahashi and Y. Hashimoto, "Intralipid Solution Mistakenly Infused into Epidural Space," *Anesthesia & Analgesia*, Vol. 71, No. 6, 1990, pp. 712-713. http://dx.doi.org/10.1213/00000539-199012000-00030

[17] R. A. Stevens and N. Jorgensen, "Successful Treatment of Dural Puncture Headache with Epidural Saline Infusion after Failure of Epidural Blood Patch. Case Report," *Acta Anaesthesiologica Scandinavica*, Vol. 32, No. 5, 1988, pp. 429-431. http://dx.doi.org/10.1111/j.1399-6576.1988.tb02760.x

[18] D. K. Turnbull and D. B. Shepherd, "Post-Dural Puncture Headache: Pathogenesis, Prevention and Treatment," *British Journal of Anaesthesia*, Vol. 91, No. 5, 2003, pp. 718-729. http://dx.doi.org/10.1093/bja/aeg231

[19] R. M. A. Moomiaie, J. Ransden, J. Stein, J. Strugar, Q. B. Zhu, J. H. Kim and J. A. Elefteriades, "Cooling Catheter for Spinal Cord Preservation in Thoracic Aortic Surgery," *The Journal of Cardiovascular Surgery*, Vol. 48, No. 1, 2007, pp. 103-108.

[20] Y. Okita, "Fighting Spinal Cord Complication during Surgery for Thoracoabdominal Aortic Disease," *General Thoracic and Cardiovascular Surgery*, Vol. 59, No. 2, 2011, pp. 79-90. http://dx.doi.org/10.1007/s11748-010-0668-x

[21] J. D. Galla, "Regional Spinal Cord Cooling Using a Countercurrent Closed-Lumen Epidural Catheter. Invited Commentary," *The Annals of Thoracic Surgery*, Vol. 80, No. 5, 2005, pp. 1833-1834.

[22] A. Mori, T. Ueda, T. Hachiya, N. Kabei, H. Okano, R. Yozu and T. Sasaki, "An Epidural Cooling Catheter Protects the Spinal Cord Against Ischemic Injury in Pigs," *The Annals of Thoracic Surgery*, Vol. 80, No. 5, 2005, pp. 1829-1833. http://dx.doi.org/10.1016/j.athoracsur.2005.04.031

[23] R. P. Cambria, J. K. Davison, S. Zannetti, G. L'Italien, D. C. Brewster, J. P. Gertler, A. C. Moncure, G. M. LaMu-

raglia and W. M. Abbott, "Clinical Experience with Epidural Cooling for Spinal Cord Protection during Thoracic and Thoracoabdominal Aneurysm Repair," *Journal of Vascular Surgery*, Vol. 25, No. 2, 1997, pp. 234-241; Discussion 241-243. http://dx.doi.org/10.1016/S0741-5214(97)70365-3

[24] R. M. Moomiaie, J. Ransden, J. Stein, J. Strugar, Q. B. Zhu, J. H. Kim and J. A. Elefteriades, "Cooling Catheter for Spinal Cord Preservation in Thoracic Aortic Surgery," *The Journal of Cardiovascular Surgery* (*Torino*), Vol. 48, No. 1, 2007, pp. 103-108.

[25] R. P. Salzano Jr., L. H. Ellison, P. F. Altonji, J. Richter and P. J. Deckers, "Regional Deep Hypothermia of the Spinal Cord Protects against Ischemic Injury during Thoracic Aortic Cross-Clamping," *The Annals of Thoracic Surgery*, Vol. 57, No. 1, 1994, pp. 65-70; Discussion 71. http://dx.doi.org/10.1016/0003-4975(94)90366-2

[26] K. Tabayashi, Y. Saiki, H. Kokubo, G. Takahashi, J. Akasaka, S. Yoshida, M. Hata, K. Niibori, M. Miura and T. Konnai, "Protection from Postischemic Spinal Cord Injury by Perfusion Cooling of the Epidural Space during Most or All of a Descending Thoracic or Thoracoabdominal Aneurysm Repair," *General Thoracic and Cardiovascular Surgery*, Vol. 58, No. 5, 2010, pp. 228-234. http://dx.doi.org/10.1007/s11748-009-0495-0

[27] W. L. Breckwoldt, C. M. Genco, R. J. Connolly, R. J. Cleveland and J. T. Diehl, "Spinal Cord Protection during Aortic Occlusion: Efficacy of Intrathecal Tetracaine," *The Annals of Thoracic Surgery*, Vol. 51, No. 6, 1991, pp. 959-963. http://dx.doi.org/10.1016/0003-4975(91)91015-N

[28] J. L. Fox, E. N. Vu, M. Doyle-Waters, J. R. Brubacher, R. Abu-Laban and Z. Hu, "Prophylactic Hypothermia for Traumatic Brain Injury: A Quantitative Systematic Review," *CJEM*, Vol. 12, No. 4, 2010, pp. 355-364.

[29] K. Peterson, S. Carson and N. Carney, "Hypothermia Treatment for Traumatic Brain Injury: A Systematic Review and Meta-Analysis," *Journal of Neurotrauma*, Vol. 25, No. 1, 2008, pp. 62-71. http://dx.doi.org/10.1089/neu.2007.0424

[30] N. G. Bazan, A. E. Musto and E. J. Knott, "Endogenous Signaling by Omega-3 Docosahexaenoic Acid-Derived Mediators Sustains Homeostatic Synaptic and Circuitry Integrity," *Molecular Neurobiology*, Vol. 44, No. 2, 2011, pp. 216-222. http://dx.doi.org/10.1007/s12035-011-8200-6

[31] R. Palacios-Pelaez, W. J. Lukiw and N. G. Bazan, "Omega-3 Essential Fatty Acids Modulate Initiation and Progression of Neurodegenerative Disease," *Molecular Neurobiology*, Vol. 41, No. 2-3, 2010, pp. 367-374. http://dx.doi.org/10.1007/s12035-010-8139-z

[32] C. Zhang and N. G. Bazan, "Lipid-Mediated Cell Signaling Protects against Injury and Neurodegeneration," *The Journal of Nutrition*, Vol. 140, No. 4, 2010, pp. 858-863. http://dx.doi.org/10.3945/jn.109.114884

[33] E. Maciá-Botejara, J. M. Morán-Penco, M. T. Espín-Jaime, F. Botello-Martínez, J. Salas-Martínez, M. J. Caballero-Loscos and M. Molina-Fernández, "Brain Lipid Composition in Rabbits after Total Parenteral Nutrition with Two Different Lipid Emulsions," *Nutrition*, Vol. 29, No. 1, 2013, pp. 313-317. http://dx.doi.org/10.1016/j.nut.2012.07.020

[34] A. M. Grunbaum, B. M. Gilfix, S. Gosselin and D. W. Blank, "Analytical Interferences Resulting from Intravenous Lipid Emulsion," *Clinical Toxicology* (*Phila*), Vol. 50, No. 9, 2012, pp. 812-817. http://dx.doi.org/10.3109/15563650.2012.731509

[35] J. Li, A. Iorga, S. Sharma, J. Y. Youn, R. Partow-Navid, S. Umar, H. Cai, S. Rahman and M. Eghbali, "Intralipid, a Clinically Safe Compound, Protects the Heart against Ischemia-Reperfusion Injury More Efficiently than Cyclosporine-A," *Anesthesiology*, Vol. 117, No. 4, 2012, pp. 836-846. http://dx.doi.org/10.1097/ALN.0b013e3182655e73

[36] G. L. Weinberg, T. VadeBoncouer, G. A. Ramaraju, M. F. Garcia-Amaro and M. J. Cwik, "Pretreatment or Resuscitation with a Lipid Infusion Shifts the Dose-Response to Bupivacaine-Induced Asystole in Rats," *Anesthesiology*, Vol. 88, No. 4, 1998, pp. 1071-1075. http://dx.doi.org/10.1097/00000542-199804000-00028

[37] G. L. Weinberg, R. Ripper, P. Murphy, L. B. Edelman, W. Hoffman, G. Strichartz and D. L. Feinstein, "Lipid Infusion Accelerates Removal of Bupivacaine and Recovery from Bupivacaine Toxicity in the Isolated Rat Heart," *Regional Anesthesia and Pain Medicine*, Vol. 31, No. 4, 2006, pp. 296-303.

[38] G. Weinberg, R. Ripper, D. L. Feinstein and W. Hoffman, "Lipid Emulsion Infusion Rescues Dogs from Bupivacaine-Induced Cardiac Toxicity," *Regional Anesthesia and Pain Medicine*, Vol. 28, No. 3, 2003, pp. 198-202.

[39] C. Jamaty, B. Bailey, A. Larocque, E. Notebaert, K. Sanogo and J. M. Chauny, "Lipid Emulsions in the Treatment of Acute Poisoning: A Systematic Review of Human and Animal Studies," *Clinical Toxicology* (*Phila*), Vol. 48, No. 1, 2010, pp. 1-27. http://dx.doi.org/10.3109/15563650903544124

[40] D. French, C. Smollin, W. Ruan, A. Wong, K. Drasner and A. H. Wu, "Partition Constant and Volume of Distribution as Predictors of Clinical Efficacy of Lipid Rescue for Toxicological Emergencies," *Clinical Toxicology* (*Phila*), Vol. 49, No. 9, 2011, pp. 801-809. http://dx.doi.org/10.3109/15563650.2011.617308

[41] J. X. Mazoit, "Cardiac Arrest and Local Anaesthetics," *Presse Medicate*, Vol. 42, No. 3, 2013, pp. 280-286.

[42] M. S. Blaber, J. N. Khan, J. A. Brebner and R. McColm, "'Lipid Rescue' for Tricyclic Antidepressant Cardiotoxicity," *The Journal of Emergency Medicine*, Vol. 43, No. 3, 2012, pp. 465-467. http://dx.doi.org/10.1016/j.jemermed.2011.09.010

[43] A. Papadopoulou, J. W. Willers, T. L. Samuels and D. R. Uncles, "The Use of Dye Surrogates to Illustrate Local Anesthetic Drug Sequestration by Lipid Emulsion: A Visual Demonstration of the Lipid Sink Effect," *Regional Anesthesia & Pain Medicine*, Vol. 37, No. 2, 2012, pp. 183-187. http://dx.doi.org/10.1097/AAP.0b013e318244b2b7

[44] J. Mauch, O. M. Jurado, N. Spielmann, R. Bettschart-Wolfensberger and M. Weiss, "Resuscitation Strategies from Bupivacaine-Induced Cardiac Arrest," *Pediatric Anesthesia*, Vol. 22, No. 2, 2012, pp. 124-129. http://dx.doi.org/10.1111/j.1460-9592.2011.03688.x

[45] J. Mauch, O. M. Jurado, N. Spielmann, R. Bettschart-Wolfensberger and M. Weiss, "Comparison of Epinephrine vs Lipid Rescue to Treat Severe Local Anesthetic Toxicity—An Experimental Study in Piglets," *Pediatric Anesthesia*, Vol. 21, No. 11, 2011, pp. 1103-1108. http://dx.doi.org/10.1111/j.1460-9592.2011.03652.x

[46] V. Montiel, T. Gougnard and P. Hantson, "Diltiazem Poisoning Treated with Hyperinsulinemic Euglycemia Therapy and Intravenous Lipid Emulsion," *European Journal of Emergency Medicine*, Vol. 18, No. 2, 2011, pp. 121-123. http://dx.doi.org/10.1097/MEJ.0b013e32834130ab

[47] P. Hamann, P. I. Dargan, N. Parbat, H. Ovaska and D. M. Wood, "Availability of and Use of Intralipid (Lipid Rescue Therapy, Lipid Emulsion) in England and Wales," *Emergency Medicine Journal*, Vol. 27, No. 8, 2010, pp. 590-592. http://dx.doi.org/10.1136/emj.2009.083352

[48] P. L. West, N. J. McKeown and R. G. Hendrickson, "Iatrogenic Lipid Emulsion Overdose in a Case of Amlodipine Poisoning," *Clinical Toxicology* (*Phila*), Vol. 48, No. 4, 2010, pp. 393-396. http://dx.doi.org/10.3109/15563651003670843

[49] D. B. Hiller, G. Di Gregorio, K. Kelly, R. Ripper, L. Edelman, R. Boumendjel, K. Drasner and G. L. Weinberg, "Safety of High Volume Lipid Emulsion Infusion: A First Approximation of LD50 in Rats," *Regional Anesthesia & Pain Medicine*, Vol. 35, No. 2, 2010, pp. 140-144. http://dx.doi.org/10.1097/AAP.0b013e3181c6f5aa

[50] G. Cave and M. Harvey, "Intravenous Lipid Emulsion as Antidote beyond Local Anesthetic Toxicity: A Systematic Review," *Academic Emergency Medicine*, Vol. 16, No. 9, 2009, pp. 815-824. http://dx.doi.org/10.1111/j.1553-2712.2009.00499.x

[51] M. Harvey and G. Cave, "Intralipid Outperforms Sodium Bicarbonate in a Rabbit Model of Clomipramine Toxicity," *Annals of Emergency Medicine*, Vol. 49, No. 2, 2007, pp. 178-185. http://dx.doi.org/10.1016/j.annemergmed.2006.07.016

[52] S. Umar, R. D. Nadadur, J. Li, F. Maltese, P. Partownavid, A. van der Laarse and M. Eghbali, "Intralipid Prevents and Rescues Fatal Pulmonary Arterial Hypertension and Right Ventricular Failure in Rats," *Hypertension*, Vol. 58, No. 3, 2011, pp. 512-518. http://dx.doi.org/10.1161/HYPERTENSIONAHA.110.168781

[53] R. Krogh-Madsen, P. Plomgaard, T. Akerstrom, K. Moller, O. Schmitz and B. K. Pedersen, "Effect of Short-Term Intralipid Infusion on the Immune Response during Low-Dose Endotoxemia in Humans," *American Journal of Physiology—Endocrinology and Metabolism*, Vol. 294, 2008, pp. E371-E379. http://dx.doi.org/10.1152/ajpendo.00507.2007

[54] K. L. Felice and H. M. Schumann, "Intravenous Lipid Emulsion for Local Anesthetic Toxicity: A Review of the Literature," *Journal of Medical Toxicology*, Vol. 4, No. 3, 2008, pp. 184-191. http://dx.doi.org/10.1007/BF03161199