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Lipid Emulsion Treatment (LET) of Post-Operative Cognitive Dysfunction (POCD)

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Abstract

Postoperative delirium (POD) or Post-operative cognitive dysfunction (POCD) is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. A new treatment for POD/POCD by intravenous Intralipid (lipid emulsion) injection in the recovery room was first suggested by Eldor on 2017 (http://medcraveonline.com/JACCOA/JACCOA-07-00273.pdf). The 4 case reports in this article describing the successful use of lipid emulsions (Smoflipid 20% and Lipidem 20%) are the first case reports of Lipid Emulsion Treatment (LET) of Post-operative cognitive dysfunction (POCD) in the medical literature.

Keywords: Post-operative Cognitive Dysfunction, POCD, Post-operative Delirium, POD, Lipid Emulsion, Intralipid, Smoflipid, Lipidem, Mitochondria.

NOTICE: All the 4 patients mentioned in this article have given their signed written permission to use their video clips taken in the recovery room for scientific purposes to all the scientific community all over the world.

Case Reports

Case 1

82 years old male, hospitalized because of abscess of the muscle on the back (thoracic part). He has type 2 diabetes, common pulmonary infection. The first surgery for abscess drainage was under local anesthesia uneventfully. He was under antibiotic (Vancomycin 1gr, Cefriaxon 1gr), Acetaminophen 1gr, Voltaren (NSAIDS) 50mg IM/day, Omeprazol 40 mg/day for 7 days.

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He had been under second surgery for larger incision to drain the abscess under balanced general anesthesia with ETT, Propofol 200 mg, Fentanyl 150mcg, Rocuronium 35 mg. Bridion 200 mg (Sugammadex) was used to reverse the residual muscle relaxant before extubation. The surgery time was 40 min.

After extubation, patient had been agitated, uncooperative, incomprehensible communication. Because he risked to falling and taking the IV line by his own, textile strings were used to tide his arms to bed. He was given 1 vial of Haloperidol IM, 2.5 mg IV bolus of midazolam, but the situation had not improved after 60 min.

We decided to start Lipid Emulsion Therapy (LET): 250ml IV Smoflipid 20% (Fresenius Kabi) over 30 min, and continued the second vial over 120 min thereafter. The effectiveness of LET: At 30 min after finishing the first 250ml Smoflipid 20%, patient was calmer, could talk with comprehensible phrases. Because he could not speak Vietnamese, so we asked his relative to communicate with him. He was cooperative, but he was a little bit relentless. The strings were released regarding his demand and lesser risk of unattended behaviours estimated by staffs. The second vial of 250 ml Smoflipid 20 % had been continued.

1) At 60 min, he was cooperative, comprehensible communication, no agitation. The strings were taken out when risk of inappropriate behaviours were lessen.

2) At 180 min (3 h), he was calm, cooperative, thirsty, hungry. We let him sitting up with the care of his relative.

3) At 240 min, Termination of the second vial of LET, he was nearly normal and had been returned to ward.

Video Clip Case 1: https://youtu.be/eNclUfCqntc

Case 2

77 years old Male admitted to hospital due to acute gangrenous cholecystitis. His past medical history was type 2 diabetes, hypertension, coronary ischemic disease, cerebral ischemic attack for 10 years ago, Parkinson. Cerebral CT Scan revealed the occupational region on the left orbit. Thoracic CT Scan also revealed a thoracic aortic aneurysm. FBC; WBC: 19.36 G/l, NEU 92.8%, Glusose: 8.2 mmol/L, Total Bilirubin: 71.72 mmol/L, Direct Bilirubin: 32.4 mmol/L, ASAT: 352 U/L, ALAST: 265 U/L, Na^+: 135 mmol/L, K: 4.2 mmol/L, Calcium: 102 mmol/L, CPR: 35.2 mg/L, CK-MB: 20 U/L, Creatinine: 1.36 mg/dL, Urea: 40.15 mg/dL, ECG: ischemic heart disease on the anterior wall. BP: 180/90 mm Hg, HR 90 BPM, BR 16, Temperature 38.5. He was fully conscious, cooperative, no localized neurologic signs, no chest pain.

He was treated by antibiotic (Meropenem 1gr IV). Because his condition was so frail so the radical surgery was not planned. The Percutaneous Transhepatic Biliary Drainage (PTBD) was proposed to relief the symptoms. He was under local anesthesia with sedative (Propofol 50mg+Fentanyl 100 mcg) with Oxygen cannula. The PTBD procedure was 30 min under the ultrasound and Fluoroscopy.

In the recovery room, his mental status was disoriented, agitated, incomprehensible communication, relentless. He was tied to the bed by strings because of falling risk.

1) We started LET by IV infusion 250 ml Lipidem 20%, (B.Braun) over 30 min. After 100 ml Lipidem 20% infused over 10 min, patient was less relentless, calmer, less agitated, communication became easier. The second vial 250 ml of Lipidem 20 % was continued in 30 min.

2) Approximately 120 min after LET, patient was not agitated, cooperative, comprehensible communication, the strings were released.

3) 4 h after LET, his mental status was nearly normal as before having surgery. He was returned to the ward. He was uneventful thereafter.

Video Clip Case 2: https://youtu.be/1Wqz4wNkhPo

Case 3

81 years old male, benign prostate enlargement hospitalized for Trans Urethral Resection of Prostate (TURP). His past medical story was hypertension, ischemic heart disease. He had closed head trauma 5 years ago, but no mental disorientation thereafter. He was cooperative, non-dependent activity in daily life.

The laboratory pre-operative tests were non-specific. Ionogram: Na 140 mmol/dL, K 3.4 mmol/dL, Cl 107 mmol/dL, Urea 52.73 mmol/dL, Creatinine 1.1 mmol/dL, Glucose 8.8 mmol/dL. ECG revealed the chronic ischemic heart disease, but the conserved heart function (Left Ventricular EF: 72%).

He was under Spinal Anesthesia for TURP. The BP before SA 180/100, HR 85 BPM, SpO_2 99 %, Midazolam 2 mg IV for sedation before SA puncture at L3-4, dose was 8 mg Heavy Bupivacaine 0.5%+20 mcg Fentanyl. The surgery time was 20 min, the irrigation solution was 1000 ml per operation, the crystalloid solution given per operation was 500 ml NaCl 0.9%, no vasoconstrictor used.

For post-operative:

1) Tramadol 100 mg IV diluted in 100 ml NaCl 0.9%, interval 8 hrs

2) Odansetron 8 mg IV

3) Omeprazol 40mg IV

4) NaCl 0.9% 1000 ml for irrigation.

3 hrs post operation, his mental status was very disorientated, agitated, yelling, screaming. The on duty anesthesiologist had used 2.5 mg Midazolam bolus + Propofol infusion to sedate him. As soon as infusion finished, the mental crisis rebound and 5 mg I.M Haloperidol was given during the night, but was not effective as the Propofol infusion.

On the next morning, his crisis rebound severely, so several nurses had to tie him to the bed.

1) We diagnosed this acute mental crisis as Postoperative Delirium. There were two possibilities that may cause POD on this patient: the TURP Syndrome and The Serotonin Syndrome (due to Tramadol).

2) We decided to use LET as challenging therapy. First vial of 250 ml Lipidem 20 % intravenously was given over 60 min.

3) After 30 min after LET, he was calm, less agitated, comprehensible communication.

4) 60 min after LET, he was calm, cooperative, comprehensible communication, he was thirsty and asked for drink.

5) 120 min after LET, the mental crisis was nearly gone, he was released from the strings, he drank and eat soft foods. The ionogram revealed the Na 131 mmol/dL, K 3.03 mmol/dL, Cl 99 mmol/dL.

6) 240 min (4h) after LET, he was a little bit more relentless, but cooperative, comprehensible communication. He complained of discomfort due to urine catheter. We decided to use the second vial of 250 ml Lipidem 20% to maintain the effectiveness.

7) 8 h from the LET, patient was calm, oriented, well communicated, comfortable, not complained on urine catheter, he drank, eaten normally.

8) No mental crisis thereafter.

Video clip case 3 : https://youtu.be/ZKOaOqdEPL0

Case 4

79 years old hypertensive female, hospitalized in emergency for biliary duct infection. Her vital signs were stable, temperature 38.5, BP 130/80, HR 80 BPM. The CT scan revealed the intra and extra hepatic biliary duct dilatation with the stone at the end of common bile duct. FBC: WBC 16 G/l, Neu 88.9%, Total Billirubin 117.2 mmol/L, direct Billirubin 70 mmol/l, AST 89UI/l, ALT 54 UI/L, Glucose 86 mg/dL, Urea 37 mg/dL, K 2.93 mmol/L, Cl 102 mmol/L, Troponin 0.024 ng/ml.

She was treated by antibiotic (Meropenem 1000mg every 8h + Metronidazole 500mg every 8 h) and was indicated for ERCP procedure. (Endoscopic Retrograde Cholangio - Pancreatography).

She was under general anesthesia with ETT. The balanced anesthesia with Propofol, Fentanyl, Rocuronium, Servoran was uneventfull, she was neutralized by Bridion 100 mg (Sugammadex) before extubation. The surgery lasted for 40 mins.

At recovery room, she was relentless, slight agitated, but not disorientated, comprehensible communication, but complained of discomfort at abdomen, not pain. The vital signs were stable. Because she was overweight and risk of falling, taking out the IV line by her own, so the strings were used to tie her arms to the bed.

We decided to use LET for this situation.

1) 250 ml Lipidem 20% was intravenously infused over 60 min.

2) After 30 min LET, her mental status seemed better, but not clear, the strings were released for her comfort

3) After 60 min LET, her mental status was improved significantly. She was less relentless, less agitated, cooperative, better communication. She asked for drink.

4) After 120 min, she was with better communication, cooperative, smiled, “did not remember what had happened before”.

5) At 180 min, the mental status was nearly the same. We decided to continue the second vial 250 of Lipidem 20% for sustainable effectiveness.

Video Clip of Case 4 : https://youtu.be/w38n8tdtQ6Y

Discussion

Post-Operative Delirium/ Post-Operative Cognitive Dysfunction

Delirium is defined by either the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [1] or by the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD 10, **Table 3**) [2]. Delirium is an acute and fluctuating alteration of mental state of reduced awareness and disturbance of attention. POD (Post-Operative Delirium) often starts in the recovery room and occurs up to 5 days after surgery [3-5]. One investigation [4] found that many patients with POD on the peripheral ward already had POD in the recovery room.

More than 230 million surgical procedures are performed each year worldwide, of which more than 80 million are in Europe [6-8]. In Europe, the in-hospital mortality rates up to a maximum of 60 days is 3% after elective surgery and nearly 10% after emergency surgery [7]. In addition to mortality, postoperative cognitive impairments such as POD and postoperative cognitive dysfunction (POCD) impose a huge burden on individuals and society [9]. The incidence of POD is dependent on perioperative and intraoperative risk factors [10]. Therefore, the incidence of POD varies within a broad range [11,12]. For example, a meta-analysis of 26 studies of POD reported an incidence of 4.0 to 53.3% in hip fracture patients and 3.6 to 28.3% in elective patients [13].

Delirium is one of the most common complications following hip fracture surgery in older people. This study identified pre- and peri-operative factors associated with the development of post-operative delirium following hip fracture surgery.

Published and unpublished literature were searched to identify all evidence reporting variables on patient characteristics, on-admission, intra-operative and post-operative management assessing incident delirium in older people following hip fracture surgery. Pooled odds ratio (OR) and mean difference of those who experienced delirium compared to those who did not were calculated for each variable. Evidence was assessed using the Downs and Black appraisal tool and interpreted using the GRADE approach.

A total of 6704 people (2090 people with post-operative delirium) from 32 studies were analysed. There was moderate evidence of nearly a two-times greater probability of post-operative delirium for those aged 80 years and over

(OR: 1.77; 95% CI: 1.09, 2.87), whether patients lived in a care institution pre-admission (OR: 2.65; 95% CI: 1.79, 3.92), and a six-times greater probability of developing post-operative delirium with a pre-admission diagnosis of dementia (OR: 6.07, 95% CI: 4.84, 7.62). There was no association with intra-operative variables and probability of delirium.

Clinicians treating people with a hip fracture should be vigilant towards post-operative delirium if their patients are older, have pre-existing cognitive impairment and poorer overall general health. This is also the case for those who experience post-operative complications such as pneumonia or a urinary tract infection [14].

Post-operative cerebral dysfunction includes delirium, usually occurring early and reversible, and post-operative cognitive disorders, usually occurring later and prolonged. This is a frequent complication in patients older than 75 years old. The two neurological pictures are often inter-related. The pathophysiology of both entities is similar and related to post-operative neuro-inflammation; therefore, onset may occur independently of any surgical complication. Post-operative cerebral dysfunction is a serious organic complication. Reduction of inflammation represents the most logical preventive measure but currently there are no studies that show this to be effective. Prevention therefore means combining several minor measures, elements that fit well into programs of enhanced post-operative recovery after surgery. Diminished pre-operative cognitive status being a major risk factor, pre-operative rehabilitation combining nutritional, physical and cognitive support can be helpful [15].

Postoperative delirium is a common and serious adverse event in the elderly patient and is associated with significant morbidity and mortality. It is of great importance to identify patients at risk for delirium, in order to focus preventive strategies. The aim of this article is to systematically review current available literature on pre-operative risk factors for delirium after vascular surgery.

A systematic literature search was conducted using PubMed and EMBASE, using the MeSH terms and key words “delirium”, “surgery” and “risk factor”. Studies were retained for review after meeting strict inclusion criteria that included only prospective studies evaluating risk factors for delirium in patients who had elective vascular surgery. Diagnosis of delirium needed to be confirmed using the Diagnostic and Statistical Manual of Mental Disorders (DSM) or ICD-10.

Fifteen articles were selected for inclusion, incidence of delirium across the studies ranged from 5% to 39%. Many factors have been associated with increased risk of delirium, including age, cognitive impairment, comorbidity, depression, smoking, alcohol, visual and hearing impairment, ASA-score, biochemical abnormalities, operative strategies and blood loss.

Delirium is a common complication after elective vascular surgery in elderly. The highest delirium incidence was observed after open aortic surgery as well as after surgery for critical limb ischemia. A picture starts to form of which predisposing factors lead to increased risk of delirium. The leading risk factors consistently identified in this systematic review were advanced age and cognitive impairment. Multi-disciplinary specialist-led interventions in the preoperative phase could decrease incidence and severity of delirium and should be focused on identified high-risk patients [16].

This study [17] investigates the relationship between cognitive dysfunction or delirium detected in the early post-surgical phase and the 1-year mortality among 514 hip fracture hospitalized older persons. Patients with early cognitive dysfunction or delirium experienced a 2-fold increased mortality risk. Early post-operative cognitive dysfunction and delirium are negative prognostic factors for mortality.

Premorbid cognitive impairment and dementia in older individuals negatively affect functional recovery after hip fracture. Additionally, post-operative delirium is an established risk factor for negative outcomes among hip fracture patients. While the majority of hip fracture patients experience minor post-surgical cognitive dysfunction, the prognostic value of this phenomenon is unknown. Therefore, we investigated the relationship between minor cognitive dysfunction or delirium detected in the early post-surgical phase and the 1-year mortality after index hip fracture.

We enrolled 514 patients with hip fracture (77.4% women), aged 65 years or older (mean age 83.1 ± 7.3 years), who underwent surgical hip fracture repair. Patients were assessed daily from the second to the fourth post-operative day and at 3, 6, and 12 months thereafter. All participants underwent comprehensive assessment, including detection of delirium by using the confusion assessment method and evaluation of cognitive function by using mini-mental state examination (MMSE; score range 0 to 30, with lower scores indicating poorer performance). In the absence of delirium, post-surgical cognitive dysfunction was defined as having low performance on MMSE. Vital status of 1 year after the index fracture and date of death were gathered from local registries.

The observed 1-year mortality rate was 14.8%. Men were more likely to die than women within 1 year of the index fracture ($p<0.01$). Compared to participants with better cognitive performance, those with MMSE <24, as well as those with delirium in the post-operative phase, showed a significantly higher 1-year mortality rate (23.3 versus 17.9 and 8.1%, respectively). Independent of age and sex, post-operative cognitive dysfunction as well as delirium was both associated with a 2-fold increased mortality risk.

The presence of minor cognitive dysfunction in the early post-surgical phase is a negative prognostic factor for mortality among elderly hip fracture patients. The burden of minor cognitive dysfunction is likely superimposed on that of delirium in subgroups of frail patients [17].

Perioperative cerebral hypo-perfusion/ischemia is a major inciting factor of postoperative delirium, which is coupled with adverse outcome in elderly patients. Cerebral oximetry enables non-invasive assessment of the regional cerebral oxygen saturation (rSO_2). This study aimed to investigate whether perioperative rSO_2 variations were

linked to delirium in elderly patients after spinal surgery.

Postoperative delirium was assessed for 48 hrs post-surgery in 109 patients aged over 60 years without a prior history of cerebrovascular or psychiatric diseases by the Confusion Assessment Method for the intensive care unit and the intensive care delirium screening checklist. The rSO2 values immediately before and throughout surgery were acquired. The preoperative cognitive functions, patient characteristics, and perioperative data were recorded.

During the 48-h postoperative period, 9 patients (8%) exhibited delirium. The patients with delirium showed similar perioperative rSO_2 values as those without, in terms of the median lowest rSO_2 values (55% vs. 56%; P=0.876) and incidence (22%, both) and duration of decline of rSO_2<80% of the baseline values. The serially assessed hemodynamic variables, haematocrit levels, and blood gas analysis variables were also similar between the groups, except for the number of hypotensive events per patient, which was higher in the patients with delirium than in those without (4, interquartile range [IQR] 3 to 6 vs. 2, IQR: 1to 3; P=0.014).

The degree and duration of decrease of the perioperative rSO_2 measurements were not associated with delirium in elderly patients after spinal surgery [18].

Three-dimensional Arterial Spin Labeling (ASL) MRI was performed before surgery in a cohort of 146 prospectively enrolled subjects ≥ 70 years old scheduled to undergo elective surgery. We investigated the prospective association between ASL-derived measures of cerebral blood flow (CBF) before surgery with postoperative delirium incidence and severity using whole-brain and globally normalized voxel-wise analysis. We also investigated the cross-sectional association of CBF with patients' baseline performance on specific neuropsychological tests, and with a composite general cognitive performance measure (GCP). Out of 146 subjects, 32 (22%) developed delirium. We found no significant association between global and voxel-wise CBF with delirium incidence or severity. We found the most significant positive associations between CBF of the posterior cingulate and precuneus and the Hopkins Verbal Learning Test-Revised total score, Visual Search and Attention Test (VSAT) score and the GCP composite. VSAT score was also strongly associated with right parietal lobe CBF. ASL can be employed in a large, well-characterized older cohort to examine associations between CBF and age-related cognitive performance. Although ASL CBF measures in regions previously associated with preclinical Alzheimer's Disease were correlated with cognition, they were not found to be indicators of baseline pathology that may increase risk for delirium [19].

Oxidative stress may be involved in occurrence of postoperative delirium (POD) and cognitive dysfunction (POCD). 8-iso-Prostaglandin F2 α (8-iso-PGF2 α), an isoprostane derived from arachidonic acid via lipid peroxidation, is considered a gold standard for measuring oxidative stress. The present study aimed to investigate the ability of postoperative plasma 8-iso-PGF2 α levels to predict POD and POCD in elderly patients undergoing hip fracture surgery.

Postoperative plasma 8-iso-PGF2 α levels of 182 patients were measured by an enzyme-linked immunosorbent assay. We assessed the relationships between plasma 8-iso-PGF2 α levels and the risk of POD and POCD using a multivariate analysis.

Plasma 8-iso-PGF2 α levels and age were identified as the independent predictors for POD and POCD. Based on areas under receiver operating characteristic curve, the predictive values of 8-iso-PGF2 α were obviously higher than those of age for POD and POCD. In a combined logistic-regression model, 8-iso-PGF2 α significantly enhanced the areas under curve of age for prediction of POD and POCD.

Postoperative plasma 8-iso-PGF2 α levels may have the potential to predict POD and POCD in elder patients undergoing hip fracture surgery [20].

Risk factors for delirium following cardiac surgery are incompletely understood. The aim of this study was to investigate whether intra-operative pathophysiological alterations and therapeutic interventions influence the risk of post-operative delirium.

This retrospective cohort study was performed in a 12-bed cardio-surgical intensive care unit (ICU) of a university hospital and included patients consecutively admitted after cardiac surgery during a 2-month period. The diagnosis of delirium was made clinically using validated scores. Comparisons between patients with and without delirium were performed with non-parametric tests. Logistic regression was applied to identify independent risk factors. Results are given as number (percent) or median (range).

Of the 194 consecutive post-cardiac surgery patients, 50 (26%) developed delirium during their ICU stay. Univariate analysis revealed that significant differences between patients with and without delirium occurred in the following intra-operative variables: duration of cardiopulmonary bypass (184 [72-299] vs 113 (37-717) minutes, p<0.001), lowest mean arterial pressure (50 [30-70] vs 55 [30-75] mmHg, p = 0.004), lowest haemoglobin level (85 [56-133] vs 98 [53-150] g/L, p = 0.005), lowest body temperature (34.5 [24.4-37.2] vs 35.1 [23.9-37.2] °C, p = 0.035), highest noradrenaline support (0.11 [0.00-0.69] vs 0.07 [0.00-0.42] μ g/kg/minute, p=0.001), and frequency of red blood cell transfusions (18 [36%] vs 26 [18%], p=0.018) and platelet transfusions (23 [46%] vs 24 [17%], p<0.001). Only platelet transfusions remained an independent risk factor in the multivariate analysis (p<0.001).

In patients undergoing cardiac surgery, various intra-operative events, such as transfusion of platelets, were risk factors for the development of a post-operative delirium in the ICU. Further research is needed to unravel the underlying mechanisms [21].

In this study, Bilge EÜ *et al*. [22] aimed to determine the risk factors and the incidence of delirium in patients who were followed postoperatively in our surgical intensive care unit for 24 hrs using the confusion assessment method (CAM).

After obtaining approval from the ethics committee, 250 patients were included in the study. Patients who were operated under general anaesthesia or regional anaesthesia and followed in the surgical intensive care unit were evaluated by the Ramsay Sedation Scale on the first postoperative day. CAM was applied to the patients who had a Ramsay Sedation Score of ≤ 4. Patients' age, gender, American Society of Anaesthesiologists (ASA) scores, preoperative risk factors, type of anaesthesia, operation time, intra-operative procedures, pain scores evaluated by the visual analogue scale (VAS) and postoperative analgesia methods were recorded.

The incidence of delirium was found to be 18.4%. The average age of patients who developed delirium was greater than the others (68.8 ± 12.7 and 57.6 ± 12, p=0.001, respectively). It was observed that a one-unit increase in the ASA score resulted in a 3.3-fold increase in the risk of delirium. The incidence of delirium in patients undergoing regional anaesthesia was 34.6%, whereas it was 16.5% in patients receiving general anaesthesia (p=0.024). The existence of preoperative diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) was shown to improve the development of delirium (p<0.05). Delirium incidence was significantly higher in patients who were administered meperidine for postoperative analgesia (p=0.013). The VAS scores of patients who developed delirium were found to be significantly higher (p=0.006).

As a result, we found that older age, high ASA score, preoperative DM and COPD are important risk factors for the development of delirium. Regional anaesthesia, high postoperative pain scores and meperidine use were observed to be associated with the development of delirium. In the postoperative period, addition of CAM, a simple measurement technique, to the daily follow-up forms can provide the early recognition of delirium, which is often underdiagnosed. We think that identification and prevention of effective risk factors have the primary importance for postoperative delirium [22].

Delirium after cardiac surgery is a major problem. The exact mechanisms behind delirium are not understood. Potential pathways of delirium include neurotransmitter interference, global cognitive disorder, and neuro-inflammation. Several predisposing and precipitating risk factors have been identified for postoperative delirium. The development of delirium following cardiac surgery is associated with worse outcomes in the perioperative period. Multiple interventions are being explored for the prevention and treatment of delirium. Studies investigating the potential roles of biomarkers in delirium as well as pharmacological interventions to reduce the incidence and duration of delirium are necessary to mitigate this negative outcome [23].

Perhaps the most frequently described mechanism of brain injury in CABG surgery is based on the recognition that micro-emboli are generated by the surgeon manipulating the heart and aorta, through cardiotomy suctioning, and by the cardiopulmonary bypass circuit itself. Micro-emboli can be detected intraoperatively as high-intensity transient signals by transcranial Doppler sonography. They have the potential to lodge in cerebral microvasculature, impairing blood supply to the brain and thus cerebral oxygenation. Several phases during cardiac surgery have been associated with increased risk of embolic showers. Aortic cannulation and clamping (during application of cardiopulmonary bypass) increase the high-intensity transient signal rate, particularly if there is extensive atheroma in the ascending aorta [24]. It is not surprising, therefore, that most (81%) micro-emboli are generated at the point of aortic cross-clamp release [25]. Retaining the shed mediastinal blood with cardiotomy suckers provides an additional source of lipid emboli and other fragments [26].

Lipid Emulsion-Mitochondrial Sink Effect

Papadopoulou A *et al*. [27] 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, cardio toxic, 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 kgs 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 colours 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 colour 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 [28] 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 μ g·kg^{-1} (group 1), Intralipid (®) 20% 4 ml·kg^{-1} (group 2), epinephrine 10 μ g·kg^{-1} + Intralipid (®) 4 ml·kg^{-1} (group 3) or 2 IU vasopressin + Intralipid (®) 4 ml·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 [29].

Local anesthetic (LA) intoxication with severe hemodynamic compromise is a potential catastrophic event. Lipid resuscitation has been recommended for the treatment 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·kg^{-1}·min^{-1} until invasively measured mean arterial pressure (MAP) dropped to 50% of the initial value. Bupivacaine infusion was then stopped, and epinephrine 3 μ g·kg^{-1} (group 1), Intralipid (®) 20% 2 ml·kg^{-1} (group 2), or Intralipid 20% 4 ml·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 (CO2) 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 (CO2) [30].

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 μ g/kg/min). Hyperinsulinemia 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 cardio toxic 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 [31].

Linoleic Acid (Main Component in Le)-Brain Mitochondria Interaction

Linoleic acid (LA; 18:2 n-6), the most abundant polyunsaturated fatty acid in the US diet, is a precursor to oxidized metabolites that have unknown roles in the brain. Here, we show that oxidized LA-derived metabolites accumulate in several rat brain regions during CO2-induced ischemia and that LA-derived 13-hydroxyoctadecadienoic acid, but not LA, increase somatic paired-pulse facilitation in rat hippocampus by 80%, suggesting bioactivity. This study provides new evidence that LA participates in the response to ischemia-induced brain injury through oxidized metabolites that regulate neurotransmission. Targeting this pathway may be therapeutically relevant for ischemia-related conditions such as stroke [32].

Long-chain polyunsaturated fatty acids like conjugated linoleic acids (CLA) are required for normal neural development and cognitive function and have been ascribed various beneficial functions. Recently, oral CLA also has been shown to increase testosterone (T) biosynthesis, which is known to diminish traumatic brain injury (TBI)-induced neuropathology and reduce deficits induced by stroke in adult rats. To test the impact of CLA on cognitive recovery following a TBI, 5-6 month old male Sprague Dawley rats received a focal injury (craniectomy+controlled cortical impact (CCI; n=17)) or Sham injury (craniectomy alone; n=12) and were injected with 25 mg/kg body weight of Clarinol® G-80 (80% CLA in safflower oil; n=16) or saline (n=13) every 48 hrs for 4 weeks. Sham surgery decreased baseline plasma progesterone (P4) by 64.2% (from 9.5 ± 3.4 ng/mL to 3.4 ± 0.5 ng/mL; p=0.068), T by 74.6% (from 5.9 ± 1.2 ng/mL to 1.5 ± 0.3 ng/mL; p<0.05), 11-deoxycorticosterone (11-DOC) by 37.5% (from 289.3 ± 42.0 ng/mL to 180.7 ± 3.3 ng/mL), and corticosterone by 50.8% (from 195.1 ± 22.4 ng/mL to 95.9 ± 2.2 ng/mL), by post-surgery day 1. CCI injury induced similar declines in P4, T, 11-DOC and corticosterone (58.9%, 74.6%, 39.4% and 24.6%, respectively) by post-surgery day 1. These results suggest that both Sham surgery and CCI injury induce hypogonadism and hypo-adrenalism in adult male rats. CLA treatment did not reverse hypogonadism in Sham (P4: 2.5 ± 1.0 ng/mL; T: 0.9 ± 0.2 ng/mL) or CCI-injured (P4: 2.2 ± 0.9 ng/mL; T: 1.0 ± 0.2 ng/mL, p>0.05) animals by post-injury day 29, but rapidly reversed by post-injury day 1 the hypo-adrenalism in Sham (11-DOC: 372.6 ± 36.6 ng/mL; corticosterone: 202.6 ± 15.6 ng/mL) and CCI-injured (11-DOC: 384.2 ± 101.3 ng/mL; corticosterone: 234.6 ± 43.8 ng/mL) animals. In Sham surgery animals, CLA did not alter body weight, but did markedly increase latency to find the hidden Morris Water Maze platform (40.3 ± 13.0s) compared to saline treated Sham animals (8.8 ± 1.7s). In CCI injured animals, CLA did not alter CCI-induced body weight loss, CCI-induced cystic infarct size, or deficits in rotarod performance. However, like Sham animals, CLA injections exacerbated the latency of CCI-injured rats to find

the hidden MWM platform (66.8 ± 10.6 s) compared to CCI-injured rats treated with saline (30.7 ± 5.5 s, $p<0.05$). These results indicate that chronic treatment of CLA at a dose of 25 mg/kg body weight in adult male rats over 1-month 1) does not reverse craniectomy- and craniectomy + CCI-induced hypogonadism, but does reverse craniectomy- and craniectomy + CCI-induced hypo-adrenalism, 2) is detrimental to medium- and long-term spatial learning and memory in craniectomized uninjured rats, 3) limits cognitive recovery following a moderate-severe CCI injury, and 4) does not alter body weight [33].

Oxidative damage of membrane polyunsaturated fatty acids (PUFA) is thought to play a major role in mitochondrial dysfunction related to Parkinson's disease (PD). The toxic products formed by PUFA oxidation inflict further damage on cellular components and contribute to neuronal degeneration. Here, we tested the hypothesis that isotopic reinforcement, by de-uteration of the bisallylic sites most susceptible to oxidation in PUFA may provide at least partial protection against nigrostriatal injury in a mouse model of oxidative stress and cell death, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. Mice were fed a fat-free diet supplemented with saturated acids, oleic acid and essential PUFA: either normal, hydrogenated linoleic (LA, 18:2n-6) and α -linolenic (ALA, 18:3n-3) or deuterated 11,11-D2-LA and 11,11,14,14-D4-ALA in a ratio of 1:1 (to a total of 10% mass fat) for 6 days; each group was divided into two cohorts receiving either MPTP or saline and then continued on respective diets for 6 days. Brain homogenates from mice receiving deuterated PUFA (D-PUFA) vs. hydrogenated PUFA (H-PUFA) demonstrated a significant incorporation of deuterium as measured by isotope ratio mass-spectrometry. Following MPTP exposure, mice fed H-PUFA revealed 78.7% striatal dopamine (DA) depletion compared to a 46.8% reduction in the D-PUFA cohort (as compared to their respective saline-treated controls), indicating a significant improvement in DA concentration with D-PUFA. Similarly, higher levels of the DA metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were detected in MPTP-exposure mice administered D-PUFA; however, saline-treated mice revealed no change in DA or DOPAC levels. Western blot analyses of tyrosine hydroxylase (TH) confirmed neuroprotection with D-PUFA, as striatal homogenates showed higher levels of TH immune-reactivity in D-PUFA (88.5% control) vs. H-PUFA (50.4% control) in the MPTP-treated cohorts. In the substantia nigra, a significant improvement was noted in the number of nigral dopaminergic neurons following MPTP exposure in the D-PUFA (79.5% control) vs. H-PUFA (58.8% control) mice using unbiased stereological cell counting. Taken together, these findings indicate that dietary isotopic reinforcement with D-PUFA partially protects against nigrostriatal damage from oxidative injury elicited by MPTP in mice [34].

Arachidonic acid (AA), 5,8,11,14-eicosateraenoic acid is abundant, active and necessary in the human body. In the present study, we reported the neuroprotective effects and mechanism of arachidonic acid on hippocampal slices insulted by glutamate, NaN_3 or H_2O_2 in vitro. Different types of models of brain injury in vitro were developed by 1mM glutamate, 10mM NaN_3 or 2mM H_2O_2. After 30 min of preincubation with arachidonic acid or linoleic acid, hippocampal slices were subjected to glutamate, NaN_3 or H_2O_2, then the tissue activities were evaluated by using the 2,3,5-triphenyltetrazolium chloride method. Endogenous antioxidant enzymes activities (SOD, GSH-PX and catalase) in hippocampal slices were evaluated during the course of incubation. MK886 (5 microM; a noncompetitive inhibitor of proliferator-activated receptor [PPAR]alpha), BADGE (bisphenol A diglycidyl ether; 100 microM; an antagonist of PPARgamma) and cycloheximide (CHX; 30 microM; an inhibitor of protein synthesis) were tested for their effects on the neuroprotection afforded by arachidonic acid. Population spikes were recorded in randomly selected hippocapal slices. Arachidonic acid (1-10 microM) dose dependently protected hippocampal slices from glutamate and H_2O_2 injury ($P<0.01$), and arachidonic acid (10 microM) can significantly improve the activities of Cu/Zn-SOD in hippocampal slices after 1h incubation. In addition, 10 microM arachidonic acid significantly increased the activity of Mn-SOD and catalase, and decreased the activities of Cu/Zn-SOD to control value after 3h incubation. These secondary changes of SOD during incubation can be reversed by indomethacine (10 microM; a nonspecific cyclooxygenase inhibitor) or AA 861 (20 microM; a 5-lipoxygenase inhibitor). Its neuroprotective effect was completely abolished by BADGE and CHX. These observations reveal that arachidonic acid can defense against oxidative stress by boosting the internal antioxidant system of hippocampal slices. Its neuroprotective effect may be mainly mediated by the activation of PPARgamma and synthesis of new protein in tissue [35].

Free fatty acid (FFA) concentrations in cerebrospinal fluid (CSF) are recognized as markers of brain damage in animal studies. There is, however, relatively little information regarding FFA concentrations in human CSF in normal and pathological conditions. The present study examined FFA concentrations in CSF from 15 patients with traumatic brain injury (TBI) and compared the data with values obtained from 73 contemporary controls. Concentrations of specific FFAs from TBI patients, obtained within 48 h of the insult were significantly greater than those in the control group (arachidonic, docosahexaenoic and myristic, $P<0.001$; oleic, palmitic, $P<0.01$; linoleic, $P<0.05$). Higher concentrations of total polyunsaturated fatty acids ($P<0.001$) and of arachidonic, myristic and palmitic acids measured individually in CSF ($P<0.01$) obtained 1 week after the insult were associated with a worse outcome at the time of hospital discharge using the Glasgow Outcome Scale. This preliminary investigation suggests that CSF FFA concentrations may be useful as a predictive marker of outcome following TBI [36].

Elevated levels of free fatty acids (FFA) have been implicated in the pathogenesis of neuronal injury and death induced by cerebral ischemia. This study evaluated the effects of immune-suppressants agents, calcineurin inhibitors and blockade of endoplasmic reticulum (ER) calcium channels on free fatty acid formation and efflux in the ischemic/re-perfused (I/R) rat brain. Changes in the extracellular levels of arachidonic, docosahexaenoic, linoleic, myristic, oleic

and palmitic acids in cerebral cortical superfusates during four-vessel occlusion-elicited global cerebral ischemia were examined using a cortical cup technique. A 20-min period of ischemia elicited large increases in the efflux of all six FFAs, which were sustained during the 40 min of reperfusion. Cyclosporin A (CsA) and trifluoperazine, which reportedly inhibit the I/R elicited opening of a mitochondrial permeability transition (MPT) pore, were very effective in suppressing ischemia/reperfusion evoked release of all six FFAs. FK506, an immunosuppressant which does not directly affect the MPT, but is a calcineurin inhibitor, also suppressed the I/R-evoked efflux of FFAs, but less effectively than CsA. Rapamycin, a derivative of FK506 which does not inhibit calcineurin, did not suppress I/R-evoked FFA efflux. Gossypol, a structurally unrelated inhibitor of calcineurin, was also effective, significantly reducing the efflux of docosahexaenoic, arachidonic and oleic acids. As previous experiments had implicated elevated Ca^{2+} levels in the activation of phospholipases with FFA formation, agents affecting endoplasmic reticulum stores were also evaluated. Dantrolene, which blocks the ryanodine receptor (RyR) channel of the ER, significantly inhibited I/R-evoked release of docosahexaenoic, arachidonic, linoleic and oleic acids. Ryanodine, which can either accentuate or block Ca^{2+} release, significantly enhanced ischemia/reperfusion-elicited efflux of linoleic acid, with non-significant increases in the efflux of myristic, arachidonic, palmitic and oleic acids. Xestospongin C, an inhibitor of the inositol triphosphate (IP_3R) channel, failed to affect I/R-evoked FFA efflux. Thapsigargin, an inhibitor of the Ca^{2+}-ATPase ER uptake pump, elicited significant elevations in the efflux of myristic, arachidonic and linoleic acids, in the absence of ischemia. Collectively, the data suggest an involvement of both ER and mitochondrial Ca^{2+} stores in the chain of events which lead to PLA_2 activation and FFA formation [37].

Brain extracellular levels of glutamate, aspartate, GABA and glycine increase rapidly following the onset of ischemia, remain at an elevated level during the ischemia, and then decline over 20-30 min following reperfusion. The elevated levels of the exocytotoxic amino acids, glutamate and aspartate, are thought to contribute to ischemia-evoked neuronal injury and death. Calcium-evoked exocytotic release appears to account for the initial (1-2 min) efflux of neurotransmitter-type amino acids following the onset of ischemia, with non-vesicular release responsible for much of the subsequent efflux of these and other amino acids, including taurine and phosphor-ethanolamine. Extracellular Ca^{2+}-independent release is mediated, in part by Na^+-dependent amino acid transporters in the plasma membrane operating in a reversed mode, and by the opening of swelling-induced chloride channels, which allow the passage of amino acids down their concentration gradients. Experiments on cultured neurons and astrocytes have suggested that it is the astrocytes which make the primary contribution to this amino acid efflux. Inhibition of phospholipase A_2 attenuates ischemia-evoked release of both amino and free fatty acids from the rat cerebral cortex indicating that this group of enzymes is involved in amino acid efflux, and also accounting for the consistent ischemia-evoked release of phosphor-ethanolamine. It is, therefore, possible that disruption of membrane integrity by phospholipases plays a role in amino acid release. Recovery of amino acid levels to pre ischemic levels requires their uptake by high affinity Na^+-dependent transporters, operating in their normal mode, following restoration of energy metabolism, cell resting potentials and ionic gradients [38].

Free fatty acid (FFA) elevation in the brain has been shown to correlate with the severity of damage in ischemic injury. The etiology of this increase in FFA remains unclear and has been hypothesized to result from phospholipase activation. This study examines the effects of specific phospholipase inhibitors on FFA efflux during ischemia-reperfusion injury. A four-vessel occlusion model of cerebral ischemia was utilized to assess the effects of PLA_2 and PLC inhibitors on FFA efflux from rat cerebral cortex. In addition, FFA efflux from non-ischemic cortices exposed to PLA_2 and PLC was measured. Concentrations of arachidonic, docosahexaenoic, linoleic, myristic, oleic, and palmitic acids in cortical superfusates were determined using high performance liquid chromatography (HPLC). Exposure to the non-selective PLA_2 inhibitor 4-bromophenylacyl bromide (BPB) significantly inhibited FFA efflux during ischemia-reperfusion injury ($P<0.01$ arachidonic, oleic and palmitic; $P<0.05$ all others); exposure to the PLC inhibitor U73122 had no observed effect. The effects of the Ca^{2+}-dependent PLA_2 inhibitor arachidonyl trifluoromethyl ketone ($AACOCF_3$) mirrored the effects of BPB and led to reductions in all FFA levels ($P<0.01$ arachidonic, oleic and palmitic; $P<0.05$ all others). Exposure to the secretory PLA_2 inhibitor 3-(3-acetamide-1-benzyl-2-ethyl-indolyl-5-oxy) propane sulfonic acid (LY311727) and to the Ca^{2+}-independent PLA_2 inhibitor bromoenol lactone (BEL) had only minimal effects on FFA efflux. Application of both PLA_2 and PLC to non-ischemic cortices resulted in significant increases in efflux of all FFA ($P<0.05$). The study suggests that FFA efflux during ischemia-reperfusion injury is coupled to activation of Ca^{2+}-dependent PLA_2 and provides further evidence of the potential neuroprotective benefit of Ca^{2+}-dependent PLA_2 inhibitors in ischemia [39].

Conclusion

The 4 case reports in this article describing the successful use of lipid emulsions (Smoflipid 20% and Lipidem 20%) are the first case reports of Lipid Emulsion Treatment (LET) of Post-operative cognitive dysfunction (POCD) in the medical literature.

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