17 October 2008

Cognitive dysfunction in anaesthesia

S Jithoo

Commentator: NF Rorke Moderator: D Singh

Department of Anaesthetics

CONTENTS

INTRODUCTION

For many years now there have been reports of changes in mental function after anaesthesia and surgery, particularly in the elderly. With a general increase in the number of elderly patients, prevalence of this phenomenon is becoming more and more important in our daily practice; therefore awareness of its existence is necessary to every anaesthetist.

Cognitive dysfunction following anaesthesia can be examined under the following broad categories: dysfunction following neurosurgery, cardiac surgery, and that following surgery in most of the other fields. Neurosurgery has obvious implications on post operative CNS dysfunction, a lot of which depends on the surgical intervention. Cognitive dysfunction following cardiac surgery has well been established and there may be a number of variables that come into play here - particularly the effects of bypass. Central vascular and carotid surgery may also constitute a separate category as the effects of cross-clamping, hypoperfusion and microemboli have significant impact on neurological function. Another syndrome of interest to us is ICU delirium.

This overview will address cognitive impairment following the general surgical disciplines.

Postoperative cognitive impairment may present as postoperative delirium and postoperative cognitive dysfunction.

DELIRIUM

The DSM4 describes delirium as

1. a change in mental status, characterised by a prominent disturbance of attention and reduced clarity of awareness of the environment and
2. it has an acute onset, developing within hours to days and tends to fluctuate during the course of the day.

This may manifest as disorientation, memory dysfunction, perceptual disturbances, mood labiality and thought disorders.

Delirium in the postoperative period can be divided into emergence delirium and post operative delirium depending on the time of presentation.

Emergence Delirium

It is observed immediately after general anaesthesia. Associated with immediate effects of anaesthetic drugs. Usually resolves within minutes to hours without long term neurological effects. Increased length of surgery has been found to be a predictor of emergence delirium. Interestingly, premedication with benzodiazepines has also been shown to increase the occurrence.[30] Emergence delirium can result in serious morbidity for the patient such as removal of intravenous lines, catheters, increased pain, bleeding and self-extubation.

Postoperative Delirium

Typically presents 24-72 hours post op following a lucid interval. It usually resolves with hours to days. Incidence rate is about 4-5% generally, 15-30% in older patients and some reports of up to 60% in elderly patients presenting for orthopaedic surgery.

Pathophysiology of Delirium

The exact cause of postop delirium remains unclear. It is a behavioural manifestation of diffuse cortical dysfunction and characterised by diffuse slowing of background activity in the EEG. It may be associated with disturbances in numerous neurotransmitters, especially acetylcholine deficiency.
Another hypothesis suggests that an increase of serum cortisol from the stress of surgery or anesthesia may be responsible.

Risk factors for Postoperative Delirium

Numerous risk factors have been found to be of importance in patients presenting with delirium.
Preoperative factors: Vision impairment, pre-existing cognitive impairment or a history of delirium, severe illness, increased urea: creatinine ratio, increasing age, history of alcohol use and preop narcotic analgesia use.
Factors during hospital stay include: malnutrition, infection, polypharmacy, physical restraints and electrolyte disturbances.
Periop risk factors : greater intraop blood loss, more post op transfusions and severe post op pain.
There are numerous **medical conditions** that may present as delirium and therefore must be excluded before a diagnosis of postoperative delirium can be made. Some of these include: infection (septicaemia, encephalitis, meningitis), metabolic causes (uraemia, liver failure, hypoglycaemia, electrolyte abnormalities), endocrine causes (Cushing's syndrome, thyroid abnormalities), intracranial pathology (tumours, raised ICP, CVA's)

nutritional (thiamine, nicotinic acid, Vit B12) and alcohol or substance withdrawal.

Drugs commonly implicated as contributors to delirium are sedatives, opioids and anticholinergics.

Table 1. Medications Associated with Delirium and Cognitive Decline

Opioid analgesics	Meperidine, fentanyl, morphine, hydromorphone
Sedative-hypnotics	Benzodiazepines, barbiturates
Antihistamines	Diphenhydramine, hydroxyzine, chlorpheniramine
Nonsteroidal inflammatory drugs	Naproxen, ibuprofen, indomethacin
Drugs affecting cholinergic transmission in the CNS	
Anticholinergics	Atropine, scopolamine
Antiparkinsonian agents	Benztropine, trihexyphenidyl, levodopa
Neuroleptics	Clozapine, thioridazine, chlorpromazine
Tricyclic antidepressants	Amitryptiline, imipramine
Class 1A antiarrhythmics	Disopyramide, quinidine, procainamide
Other cardiac medications	Digoxin, beta-adrenergic, antagonists, methyldopa
Gastrointestinal H2-antagonists	Cimetidine, ranitidine

CNS=central nervous system.

Table 1. Drugs commonly associated with Delirium[15]

Presence and severity of **post operative pain** has been directly linked with postoperative delirium. Opioids have been known to increase the risk of delirium therefore a multimodal opioid sparing approach may have benefit. The various opioids have been compared and two studies[15] found pethidine, which is commonly used in our setting for postop analgesia, to be associated with a higher incidence when compared to other opioids.

There have been numerous studies comparing the incidence of postop delirium in general and regional anaesthesia and surprisingly, majority of the studies found no significant difference between the two.[11,25]

Assessment of Delirium

A number of scales and systems have been devised to assess the presence of delirium.

The most widely used tool is the Confusion Assessment Method. This test exams 4 different aspects to make the diagnosis of delirium. (Table 2). The diagnosis requires the presence of features 1 and 2 and either 3 or 4. Concurrent validation with psychiatric diagnosis revealed sensitivity of 94-100% and specificity of 90-95% and closely correlates with DSM-IV criteria for delirium. The tool can be administered in less than 5 minutes. It identifies the presence or absence of delirium but does not assess the severity of the condition, making it less useful to detect clinical improvement or deterioration.

Other methods sometimes referred to include the Delirium Rating Scale, Delirium Symptom Interview, the MMSE and the Riker Scale. The lack of a single assessment tool often delays the diagnosis and treatment of postop delirium and therefore the incidence may in fact be greater than that reported.

The Confusion Assessment Method (CAM) Diagnostic Algorithm

Feature 1: *Acute Onset and Fluctuating Course*
This feature is usually obtained from a family member or nurse and is shown by positive responses to the following questions: Is there evidence of an acute change in mental status from the patient's baseline? Did the (abnormal) behaviour fluctuate during the day, that is, tend to come and go, or increase and decrease in severity?

Feature 2: *Inattention*
This feature is shown by a positive response to the following question: Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

Feature 3: *Disorganized thinking*
This feature is shown by a positive response to the following question: Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

Feature 4: *Altered Level of consciousness*
This feature is shown by any answer other than "alert" to the following question:: Overall, how would you rate this patient's level of consciousness? (alert [normal]), vigilant [hyperalert], lethargic [drowsy, easily aroused], stupor [difficult to arouse], or coma [unarousable])

The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4.

Table 2. Confusion Assessment Method[17]

Consequences of Postop Delirium

It is directly associated with an increased risk of morbidity and mortality. Symptoms are often worse at night. Patients can cause **severe injury** to themselves. They may also pose a threat to other patients, visitors and staff. Alternatively, it can present as a hypoactive form and may often go undiagnosed or be confused with depression. Patients are less likely to comply with taking **medication** which may worsen pre-existing conditions

or interfere with adequate **pain control**. More intensive **nursing care** is often needed as well as consultations from other **medical disciplines**, more **investigations** and greater **drug use**. Post operative **mobilisation** and physiotherapy may also be affected. **Duration of hospital stay** is almost always increased and additional **costs** to patients and hospitals are inevitable due to any of the above factors.

Prevention and Treatment of Postop Delirium

What can we do to reduce the incidence of this syndrome?

- Identify patients at greater risk and minimize risk factors that can be altered.
- Perioperative orientation programs seem to have a great effect. This includes preoperative counselling and postoperative programs. In the Western world and Europe, the most widely used post operative intervention in the elderly is the Hospital Elder Life Programme**.**

  Six risk factors for delirium are targeted for intervention: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. These factors were selected on the basis of evidence of their association with the risk of delirium and because they were amenable to intervention strategies. Numerous non-pharmacological interventions are used (Table 3) and have been shown to significantly reduce the incidence of delirium in the elderly. Attempts must be made to avoid the use of physical restraints as this may worsen the agitation.
- Treat any obvious conditions that can manifest as delirium before simply attributing it to the post op period and the effect of drugs.
- Pharmacological intervention is usually the last resort if other measures fail to decrease agitation. The suggested agent for acute agitation is haloperidol 0.5-1mg iv every 5-10min until agitation settles. IM doses may also be given – 2-10mg waiting 60-90 min between doses.[11] Haloperidol may treat acute agitation but has not been shown to limit the duration of PD. Benzodiazepines may be considered but is said to occasionally have a paradoxical effect in elderly patients and may worsen agitation. It is useful if alcohol withdrawal is the cause of the delirium. Newer atypical antipsychotics are such as olanzepine are now also being used with good effect.

Table 3 Risk Factors for Delirium and Intervention Protocols.

Targeted Risk Factor and Eligible Patients	Standardized Intervention Protocols	Targeted Outcome for Reassessment
Cognitive impairment* All patients, protocol once daily; patients with base-line MMSE score of <20 or orientation score of <8, protocol three times daily	Orientation protocol: board with names of care-team members and day's schedule; communication to reorient to surroundings Therapeutic-activities protocol: cognitively stimulating activities three times daily (e.g., discussion of current events, structured reminiscence, or word games)	Change in orientation score
Sleep deprivation All patients; need for protocol assessed once daily	Nonpharmacologic sleep protocol: at bedtime, warm drink (milk or herbal tea), relaxation tapes or music, and back massage Sleep-enhancement protocol: unit-wide noise-reduction strategies (e.g., silent pill crushers, vibrating beepers, and quiet hallways) and schedule adjustments to allow sleep (e.g., rescheduling of medications and procedures)	Change in rate of use of sedative drug for sleep†
Immobility All patients; ambulation whenever possible, and range-of-motion exercises when patients chronically non-ambulatory, bed or wheel-chair bound, immobilized (e.g., because of an extremity fracture or deep venous thrombosis), or when prescribed bed rest	Early-mobilization protocol: ambulation or active range-of-motion exercises three times daily; minimal use of immobilizing equipment (e.g., bladder catheters or physical restraints)	Change in Activities of Daily Living score
Visual impairment Patients with <20/70 visual acuity on binocular near-vision testing	Vision protocol: visual aids (e.g., glasses or magnifying lenses) and adaptive equipment (e.g., large illuminated telephone key-pads, large-print books, and fluorescent tape on call bell), with daily reinforcement of their use	Early correction of vision, ≤48 hr after admission
Hearing impairment Patients hearing ≤6 of 12 whispers on Whisper Test	Hearing protocol: portable amplifying devices, earwax disimpaction, and special communication techniques, with daily reinforcement of these adaptations	Change in Whisper Test score
Dehydration Patients with ratio of blood urea nitrogen to creatinine≥18, screened for protocol by geriatric nurse-specialist	Dehydration protocol: early recognition of dehydration and volume repletion (i.e., encouragement of oral intake of fluids)	Change in ratio of blood urea nitrogen to creatinine

*The orientation score consisted of results on the first 10 items on the Mini–Mental State Examination (MMSE).

†Sedative drugs included standard hypnotic agents, benzodiazepines, and antihistamines, used as needed for sleep.

Preoperative assessment
Detailed history of drugs
Medical problem evaluation
Detection of sensory or perceptual deficits
Detection of cognitive impairment by neuropsychologic testing*
Mental preparation (orientation and communication) before to surgery†
Use of geriatric-anesthesiologic programme‡
Intraoperative precautions
Adequate oxygenation and perfusion
Correct the electrolyte imbalance
Adjust drug dose
Minimize the variety of drugs
Avoid atropine, flurazepam, scopolamine
Postoperative care
Environmental support
Well-lit cheerful room
Quiet surroundings
Keep patient oriented
Visit by friend or family
Pain control
Postoperative intervention (hearing aid, vision aid, non-pharmacological sleep aid, early mobilization, correction of dehydration)†
Identify risk-associated drugs
Anticholinergics
Depressants
H_2-antagonists
Reassure patient and family

Table 4. Prevention of Postoperative Delirium[16]

POST OPERATIVE COGNITIVE DYSFUNCTION

Cognition is used to describe the processes of perception, memory and information processing allowing one to acquire knowledge, solve problems and plan for the future. The term postoperative cognitive dysfunction (POCD) therefore describes impairment of one or more of these processes following surgery and anaesthesia

Diagnosis

There is still no standardized definition of POCD making diagnosis and research difficult. A comprehensive assessment of cognitive function requires a battery of tests assessing a variety of different aspects. Patients have to be assessed pre and postoperatively as without a baseline level, it would not be possible to associate low postoperative function to surgery or anaesthesia.

There are numerous different tests used by different centres and researchers.(Table 5) The timing of tests is also quiet inconsistent varying from few hours to months after surgery. The general consensus seems to be that early POCD is present at 1 week and late POCD at about 3months and after.

Tests used in cognitive battery

1. Trail making A
2. Trail making B
3. Symbol digit modality
4. Digit span forwards
5. Digit span backwards
6. Selective reminding
7. Visual gestalts learning
8. Visual gestalts recall
9. Picture recognition learning
10. Picture recognition recall
11. WAIS block design
12. Sorting test (willanger)
13. Reaction time
14. Tapping
15. Card sorting
16. Immediate free recall
17. Delayed free recall
18. Delayed recognition
19. Paired association learning
20. Addition
21. Stroop colour word interference
22. Story recall
23. Visual memory tests
24. Object learning test
25. Digit copying test (DCT)
26. Controlled oral word association test
27. Finger oscillation test
28. Two point discrimination test
29. Hand preference
30. Verbal recall – Rivermead behavioural memory test (PRT)
31. Verbal learning – Fuld object memory test (FOMTL)
32. Tactile naming (FOMTN)
33. Symbol cancellation
34. Boston naming test
35. Digit symbol from WAIS
36. Benton visual retention
37. Benton visual recognition
38. Mattis Kovner verbal recall
39. Mattis Kovner verbal recognition

Table 5. Types of tests used in assessment of POCD

Predictors and Incidence of POCD

Advancing age: One of the largest studies done regarding the subject was the ISPOCD1 (International Study of Post Operative Cognitive Dysfunction).[2]

1218 patients older than 60yrs were evaluated. They found the incidence of POCD to be **25.8% 1 week after surgery** and about **9.9% 3 months later**. Various other studies reported a similar incidence; the most recent involving 1064 patient 18yrs and older undergoing major non-cardiac surgery[1]. Findings showed 30 – 40% of adults from all age groups experienced POCD at discharge. All patients had improvement of cognitive function by 3 months but the prevalence of late POCD (persisting after 3 months) was significantly greater (12.7%) in the elderly population(>60yrs) when compared to young age group - 18-39yrs (5.7%) and middle aged - 40 – 59yrs (5.6%).

Although it is well known that there is a gradual decline in cognitive function during normal aging, some patients seem at greater risk for a more rapid decline after surgery.

Ageing is known to cause several structural changes to brain tissue which are likely to be correlated with a reduction in cognitive reserve. Is the deterioration seen in postoperative patients initiated by an exacerbation of processes already active during the aging process? If so, does surgery or anaesthesia accelerate these mechanisms?

Lower educational levels: This has also been associated with prolonged POCD. It was first reported as a risk factor in the ISPOCD1 investigation and supported by Monk's trial.

History of CVA: Interestingly Monk also showed that patients with a previous history of a CVA who made full recovery with no residual effects were more at risk of development of POCD. This may support the theory that a decreased cognitive reserve predisposes patients.

Type of surgery: Type of surgery may also play as role. Cardiac and neurosurgery are well established as high predictors.

Major surgery and in-patient vs. outpatient surgery may also increase the risk in early POCD. However, little difference was found at 3months. The effect on the incidence on early POCD could be related to numerous factors like duration of surgery and anaesthesia, post op complications, metabolic stress response and hospitalisation. Features of the hospital setting such as noise, immobilization, isolation and sleep deprivation may contribute to a sensory overload especially in the elderly.

Other predictors that have been considered as risk factors in early POCD but with little evidence include **duration of anaesthesia**, **post op respiratory complications**, **infections**, **second operation within 1 week** and **biomarkers: elevated levels of stable nitric oxide.**

Aetiology

The aetiology of POCD remains undetermined.

Among the theories explored are:

Intra or post operative hypotension – This was one of the hypotheses of the ISPOCD1 trial. Episodes of hypotension were thought to cause ischaemia later manifesting as cognitive decline. However, despite high rates of profound hypotension in many patients, no correlation could be made with POCD.

Intra and post operative hypoxia – This was examined in the ISPOCD1. Patients were monitored up to 3 days post operatively with continuous pulse oximetry. Yet again there was no link that could be made with episodes of hypoxia and POCD.

Cortisol levels of patients were examined in view of the fact that elevated cortisol levels effects cognition. The stress response of surgery does cause elevated levels but this was not responsible for cognitive changes. There was an alteration in the diurnal variation of cortisol secretion seen in some patients developing POCD but no clear evidence was found to label it a causative agent.

Microemboli causing cognitive dysfunction may play a large role in cardiac surgery. Although present in many patient undergoing noncardiac surgery, embolism counts were low and no link to POCD could be made.

Genetic predisposition - Patients with the E4 allele of the ApOE gene are known to have worse cognitive and neurological outcomes after brain injury and stroke and to have a greater risk of Alzheimer's disease but this has not proved to be a marker for POCD.

Neuroinflamation is another suggested contributor to POCD. Increased levels of pro inflammatory cytokines including IL6 and PGE2 have been found in CSF after non-neuro, non-cardiac surgery. Animal studies supporting this found inflammation in hippocampal tissue postoperatively. Inflammatory changes in these regions are capable of adversely affecting learning and memory as well as other cognitive domains. Whether this inflammatory process is due to anaesthesia, surgery or both has yet to be determined

The question remains, does anaesthesia per say cause cognitive dysfunction.

The most obvious would be to look at general anaesthesia. This seems a very plausible theory given the profound effects of general anaesthetic

drugs on the CNS. However the clinical evidence for this is relatively sparse. Most results come from evidence found in animal studies. Important findings were:

- Rats exposed to desflurane were found to have persistent changes in brain protein expression.
- Other studies found that isoflurane-nitrous oxide anaesthesia without surgery impairs spatial learning for weeks in aged rats.
- Anaesthetic induced neuroapoptosis occurs in cell cultures after exposure to clinically relevant doses of isoflurane as well as in brains of old rats after nitrous oxide and ketamine.

Although we cannot directly extrapolate animal studies to the human brain without further research, these findings are of some concern.

However, before we can attribute POCD to general anaesthesia, we have to look at results comparing the incidence of POCD in regional and general anaesthesia.

- In 1995, JAMA, Williams compared general vs. epidural anaesthesia for knee replacement in older patients in a randomized controlled trial involving 262 patients. He found the incidence of POCD to be similar in both groups.[26]
- In 2004, Wu provided a review of 24 studies evaluating the choice of anaesthesia and also concluded no difference.[28]
- More recently in 2006, 18 studies were evaluated by Bryson et al and again, the type of anaesthesia was found not to make a difference regarding the incidence of POCD.[31]

However one confounder is that IV sedation was often used during regional procedures.

In all likelihood, the aetiology of POCD is a **multifactorial** one. How much of this can be attributed to anaesthetic drugs has yet to be determined.

Effects of POCD

Classification of types of dysfunction experienced by patients[6]

- 53% experienced problems with what is described as the memory domain i.e. the capacity for learning and remembering.
- 34% had difficulty with the executive function domain i.e. our ability to efficiently process information, concentrate, and self-monitor.
- 13 % experienced a combination of both.

Anatomically these areas are represented by the hippocampus, thalamus, and basal forebrain, the prefrontal cortices, thalamus and white matter.

Effects in daily life

These effects can manifest as problems with commuting, shopping, grooming, meal preparation, housework, medication and managing finances.

Depending on the type and severity of cognitive dysfunction, it my have impact on daily functioning, ability with work, interaction with friends and family. It may also necessitate additional care or home placement needed for those affected which could have financial and emotional implications on families.

Long term outcome

Long term follow up of patients with POCD showed that at 1-2 yrs the incidence was only about 1 % suggesting some element of reversibility.[18] Further work needs to be done to confirm this incidence.

However what have raised some eyebrows was the findings of Monk et al also published this year in which he found an increased 1 yr mortality rate with patients with POCD at discharge and at 3months. No causal link could be found but this certainly asks more questions.

THE DEVELOPING BRAIN

Although much of the research regarding the effects of anaesthesia has been done on the elderly, there is growing concern regarding the effects of anaesthesia on the paediatric population.

Again here, much of the research has been done on animal models but certainly has generated great interest. Interesting results include:

- Interference in the action of certain neurotransmitters during a critical stage of brain development can trigger apoptosis of a large number of neurons. In the human this correlates to the period from 6months of pregnancy to third year after birth – a period known as synaptogenesis. Apoptosis can be triggered by transient blockade of NMDA receptors or excessive activation of GABA receptors. This is the action of many for our anaesthetic agents**.** It is therefore postulated that exposure to these drugs, even as a single event can cause degeneration in the young brain. A similar effect has been proven with alcohol giving rise to Foetal Alcohol Syndrome. Alcohol is a potent NMDA antagonist and GABA agonist.[23]
- Another study, reported apoptosis in neonatal rats exposed to 6 hrs of anaesthesia using isoflurane, N2O and midazolam. Neither N2O nor midazolam on there own produced apoptosis whereas isoflurane did.

However the combination of these agents produced a greater increase in apoptotic degeneration.[23]
Primate studies have been the next phase and are currently underway with ketamine.
How much of these in-vitro studies can be extrapolated to human babies remains to be seen but have raised concern.
Will it mean us having to delay elective paediatric surgery in the future till after 3yrs of age?

OCCUPATIONAL EXPOSURE

If there is some truth to the effects of anaesthetic agents used, one must ask what about long term neurological effects for theatre personnel chronically exposed to these agents.
Contamination of our theatres with volatile agents is still present despite improvements in scavenging systems.
Common complaints from staff include disorientation, headaches, mood disorders, and slower reaction time.

In 2005, Vouriot el al explored the chronic exposure effects of anaesthetic gases on postural control in theatre personnel. Staff exposed to gases for 5 yrs or more showed a significant impairment in static and dynamic balance.[7]
There has also been suggestion that with long term exposure, isoflurane and halothane may increase the accumulation of B-amyloid peptide- a hallmark in the pathogenesis of Alzheimer's disease.[8]

CONCLUSION

So in conclusion, the jury is still out on a number of issues regarding dysfunction and anaesthesia.
Post op delirium is a definite entity that can have immediate effects on patient morbidity.
POCD does exist, particularly in the elderly. However there is still much speculation of the exact cause, whether it may be anaesthesia, surgery or a combination of both. Still more research is needed here. The question of occurrence of POCD with regional anaesthesia complicates the matter even further. The effect of anaesthetic drugs on the developing brain as well as the result of chronic exposure is also of concern.
Because the mechanism of POCD remains largely uncertain, it is difficult to recommend specific prevention or treatment strategies. There is not enough evidence right now for us to change our anaesthetic practice but we need to be aware of these potential issues and look out for upcoming research.

REFERENCES

1. *Monk et al: Predictors of Cognitive Dysfunction after Major Noncardiac Surgery. Anaesthesiology 2008 108:18-30*
2. *Moller JT et al: Long-term postoperative cognitive dysfunction in the elderly.*
   Lancet 1998;352:857-61
3. *Rasmussen et al: Is peri-operative cortisol secretion related to postoperative cognitive dysfunction. Acta Anaes Scand 2005;49:1225-1231*
4. *Koch S et al: Cerebral Fat Microembolism and Cognitive Decline After Hip and Knee Replacement:. Stroke 2007;38-3:1079-81*
5. *Abildstrom H et al: Apolipoprotein E genotype and cognitive dysfunction after noncardiac surgery. Anaesthesiology 2004;101:855-61*
6. *Price C et al: Type and Severity of Cognitive Decline in Older Adults after Noncardiac Surgery. Anesthesiology 2008; 108 (1) pp 8-17*
7. *Vouriot A et al : Chronic exposure to anaesthetic gases affects balance control in operating room personnel. Neurotoxicology 2005; 26:193-8*
8. *Eckenhoff RG et al: Inhaled anaesthetic enhancement of amyloid-beta oligomeristaion and cytotoxicity. Anaesthesiology 2004;101:705-9*
9. *Dodd C: Post operative cognitive deficit in the elderly surgical patient. British Journal of Anaesthesia 1998; 81:449-462*
10. *Hanning CD: Postoperative cognitive dysfunction. British Journal of Anaeshesia 2005; 95: 82-87*
11. *Silverstein J, M.D., Matthew Timberger, B.A. ,David L Reich,M.D., Susan Uysal,: Central Nervous System Dysfunction after Noncardiac Surgery and Anaeshesia in the elderly. Anaesthesiology 2007;106; 622-8*
12. *Cook D, Rooke A : Priorities in Perioperative geriatrics. Anaesthesia Analg 2003; 96;1832-36*
13. *Linnea E Vaurio, BA, Laura P Sands, Ph.D., Yun Wang, Ph.D.,E Ann Mullen,Bsc., Jacqueline M. Leung, MD, MPH. Postoperative Delirium: The importance of pain and pain management. Anaesthesia Analg 2006; 102:1267-73*
14. *Punit T Sharma, MD,FE Sieber, MD, KJ Zakriya MD, RWPauldine, MD, KB Gerold, DO, J Hiang, MD, and TH Smith, CRNA. Recovery Room Delirium Predicts Postoperative Delirium after hip-fracture repair. Anaesthesia Analg 2005;101:1215-20*
15. *HK Fong, MD,Laura P Sands, Ph.D., Jacqueline M. Leung, MD, MPH.The role of Postoperative Analgesia in Delirium and Cognitive decline in elderly patients: a systemic review. Anaesthesia Analg 2006;106:1255-66*

16. *F. Jin and F Chung. Minimizing perioperative adverse events in the elderly. British Journal of Anaesthesia 87 (4): 608-24*
17. *Christine M. Waszynski RN, C, MS:Confusion Assessment Method (CAM) Dermatol Nurs 16(3):309-310, 2004*
18. *Abildstrom H. Cognitive dysfunction 1-2 years after noncardiac surgery in the elderly. Acta Anaesthesiol Scand 2000; 44: 1246-1251*
19. *Tim Johnson F.R.C.A. Postoperative cognitive dysfunction in middle-aged patients. Anaesthesiology 2002; 96:1351-7*
20. *J. Canet. Cognitive dysfunction after minor surgery in the elderly. Acta Anaesthesiol Scand 2003; 47:1204-1210*
21. *Kathleen Franco. The cost of Delirium in the surgical patient. Psycosomatics 42:1, January- February 2001*
22. *Sharon K Inouye, M.D. A multicomponent intervention to prevent delirium in hospitalized older patients. NEJM 04/03/1999; 340:669-679*
23. *Anand,Kanwaljeet J.S. M.B.B.S,D.Phil. Anesthetic agents and the immature brain: Are these toxic or therapeutic? Anaesthesiology : Vol 101(2)August 2004 :527-530*
24. *Olney, John W. M.D.*; Anesthesia-induced Developmental Neuroapoptosis: Does It Happen in Humans? Anesthesiology: Volume 101(2)August 2004pp 273-275*
25. *Frances F. Chung, M.D. Postoperative Delirium in the Elderly. American society of anesthesiologists. – Syllabus on geriatric Anesthesiology.*
26. *Williams-Russo P: Cognitive effects after epidural vs. general anesthesia in older adults. A randomized trial. JAMA : 1995;274(1)*
27. *Rasmussen LS: Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 2003; 47:260-266*
28. *Wu C: Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Regional Anaesthesia and Pain Medicine 2004; 29(3):257-268*
29. *Mellon R et al: Use of Anesthetic Agents in Neonates and Young Children. : Anaesth Analg 2007; 104(3): 509-520*
30. *Lepouse C et l: Emergence delirium in adults in the post-anaesthesia care unit. BJA 2006; 96(6):747-53*
31. *Bryson G: Evidence-based clinical update: General anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anaesth 2006;53(7):669-677*
32. *Zuccherelli L: Killing me Softly? The long-term effects of anaesthesia. SAJAA 2007;13(6)5-10*
33. *Maze M: Taking the lead in research into postoperative cognitive dysfunction. Anaesthesiology 2008;108:1-2*

34. *McGoldrick K: The graying of America. Anaesthesia for the geriatric outpatient. American Society of Anaesthesia Refresher 2006:212*
35. *Crosby C: Anaesthesia, aging and the brain.. American Society of Anaesthesia Refresher 2006:302*

NOTES