Opioid free anaesthesia (OFA)

Why & How OFA? Brugge 2014 J P Mulier, MD PhD

Before the opioid introduction in 1960, hypnosis, immobility and hemodynamic stability were achieved with deep inhalation or high dose hypnotics like pentothal. These agents induced strong hemodynamic suppression. Therefore the introduction of balanced anaesthesia was a gift. Opioids induced hemodynamic stability by suppressing the sympathetic system. Opioids are the strongest analgesics and therefore analgesia became an essential part of balanced anaesthesia next to hypnosis and immobility.

Is it time today to enhance this vision? At least Paul Janssens founder of Janssens Pharmaceuticals, who invented all synthetic opioids, warned 20 years ago that the medical use of their formulated Remifentanyl can cause addiction, immunosuppression and other long term effects that were not obvious at that time. Nevertheless all anaesthesiologists got attracted to these very strong opioids by its seemingly very short activity. Moreover the combination with low dose new intravenous hypnotics without inhalation agents became again attractive to avoid PONV and retain hemodynamic stability. Side effects of the inhalation agents were avoided but are the side effects of the opioids not more dramatic and more prolonged?

Do we need to avoid the opioids peroperative? Why?

Most common side effects of opioids are well known like respiratory depression, pruritus, nausea and vomiting, ileus, constipation, urinary retention, tolerance by desensitisation, reduced cardiac output, dizziness, somnolence and short duration of central muscle stiffness. A less known side effect is pharyngeal muscle weakness giving obstructive breathing and should be avoided in obese patients[1] [2] [3]. A recent guideline of the ASA recommends avoidance or minimizing of perioperative use of respiratory depressants in patients with obstructive sleep apnea.[4]

Several reasons are added every year to reduce or avoid the use of synthetic opioids. Enhanced recovery after surgery advocates the strong reduction of opioids postoperative to improve the healing and to avoid the suppression of the immunologic system. If no opioids are used during surgery, less opioids are needed to achieve a pain free recovery, as addiction did not destroy yet our mu receptor system. Oncologic patients have a better survival when no opioids are used during surgery and brain dysfunction is certainly less in neonates.[5] [6] POCD seems to be also lower and patients have a more natural sleep form the first postoperative day.
Opioid induced hyperalgesia and chronic pain syndromes are more frequent when high dose opioids are used per operative.[7]

Post-operative needs are different from per-operative needs.

Analgesia, or being pain free, is only important post-operative when patients are awake. Per-operative we need a stress free anaesthesia or a sympathetic block to achieve hemodynamic and other organ stability. What actually counts is supporting the function

of all organs by guaranteeing a sufficient tissue perfusion to provide nutrients and oxygen and to remove carbon dioxide and waste. Opioids were the ideal agents to achieve these needs in the past but today it is possible without them. But is the outcome also better without opioids?

Hypnosis only is not enough but awareness is what patients are most afraid and therefore amnesia is what should be achieved with hypnosis. Immobilization is what was needed most frequently. Several acts like intubation and laparoscopy might require deep muscle relaxation. Deep hypnosis or high dose opioids can improve immobilization and block respiration but will never give the same muscle relaxation as achieved by neuromuscular blocking agents. Therefore muscle relaxation and not immobilization remains an essential part of many anaesthetics.

A new approach?

The new approach in anaesthesia should mention hypnosis with amnesia, sympathetic stability to protect organs and provide sufficient tissue perfusion and muscle relaxation at the moment that anaesthesiologist and surgeons require it. It is also important to reduce postoperative cognitive dysfunction. This is a frequent problem after balanced anaesthesia with inhalation and TIVA as both use opioids in moderate or large amounts. Using Xenon instead does not reduce POCD probably due to the opioids[5].

Avoiding opioids during anaesthesia is possible without hemodynamic instability. We need to stabilize the sympathetic system and avoid cardio vascular instability. Opioids in high dose were the ideal agents to achieve this stability.

Their introduction was important because the hypnotics at that time were strong cardiovascular depressant agents and al lot of patients had unknown and untreated cardiovascular coronary diseases. Giving high doses of opioids allowed the reduction of hypnotics and muscle relaxants. Today we have safe hypnotics and neuromuscular blocking agents that can be used to achieve a sufficient depth of hypnosis and muscle relaxation and most patients are treated for their cardiovascular problems.

Today we also have drugs that stabilize the sympathetic system and given together in a multimodal approach you can avoid opioids at all.
A sympathetic blockade per-operative and a multimodal approach of non opioid analgesics starting per-operative are needed to reduce and frequently avoid any opioid use at all postoperative. This can be called the opioid paradox, the more opioids you give per-operative the more opioids you need to give postoperative or the higher the pain scores will be.

The best indications for this opioid free anaesthesia (OFA) today are obese patients, patients with obstructive sleep apnoea syndrome (OSAS), opioid addiction, hyperalgesia problems and chronic pain syndromes better known as Complex regional pain syndromes (CRPS) (previously described as Causalgia, Suddeck's atrophy, Raynaud syndrome and reflex sympathetic dystrophy). Sympathicus block is the standard treatment in this group of patients and why should we not extend their treatment during anaesthesia when the risk for sympathic stress is increased.

Possible relative contraindications are nodal block and the disorders of autonomic failure better known as orthostatic hypotension (Multiple System Atrophy). Patients with a known critical coronary stenosis or an acute coronary ischemia should not receive an opioid free anaesthesia for the moment. Opioid free anaesthesia should also be avoided in non-stabilized hypovolemic shock and poly-trauma patients as peripheral vasodilation can limit the perfusion of critical central organs while opioids induce vasoconstriction.

Controlled hypotension for minimal blood loss in the operation field requires a cardiac output depression. This is easier achieved with high dose remifentanyl than with the vasodilation medications of the opioid free method. If opioid free is used additional drugs are required to reduce the cardiac output, like B blockers. Vasoconstrictors to reduce CO will stimulate most of the time also the cardiac contraction directly and indirectly by an increased myocardial perfusion. Moreover the vasoconstriction takes places in a vascular bed of non-critical organs like the splanchnic circulation increasing further the perfusion of brain and head region where most of the time controlled hypotension is required.

Daily practice in Bruges

Today many anaesthetics are given in Sint Jan Bruges without any opioids per operative and patients love it as they have less pain postoperative, sleep better the first night and do not suffer from opioid side effects like PONV, itching or respiratory depression. Nurses on the ward recognize postoperative immediate the patients who got OFA and patients question why they should remain in bed the day of operation while they feel good to walk around. They can get early out of bed but never alone as orthostatic hypotension is more frequent due to sympathetic block.

In spring 2011 OFA was introduced in Bruges with a very low dose ketamine, clonidine and B blockade. Local wound infiltration was added. Inhalation was easiest as hypnotic, the dose of Propofol was too high to achieve sufficient hypnosis without opioids.

Beginning of 2012 dexmedetomidine became available in Europe changing our approach first by adding dexmedetomidine in infusion during surgery and next replacing clonidine at induction. 0,6 to 1 mac of inhalation anaesthetics is added to achieve hypnosis without awareness. Lidocaine and Magnesium at induction and by infusion improved further the multimodal approach. When paracetamol and ketorolac or diclofenac is added during surgery a perfect postoperative pain treatment is possible without opioids or epidurals even in large laparotomies. For CRPS patients we continue a lower dose of dexmedetomidine giving no sedation together with Lidocaine, Ketamine and magnesium. Inhalation remains easier to control the hypnosis as inhalation agents work on all human cells while Propofol act only on the central brain. Using Propofol combined with sympathetic block is possible but requires very high Propofol doses while inhalation can be given below 1 MAC value. A possibility is to give the full dose of dexmedetomidine at 1 or 1.2 ug/kg/h. However rapid awakening after this dose of dexmedetomidine is not possible for a procedure of a few hours making this method not practical either.

The respiratory centre is not depressed when avoiding opioids. Pressure support ventilation, being more natural and driven by the patients needs is always possible under opioid free, even when high dose muscle relaxants are given if required by the surgical procedure and the abdominal compliance. This is a real advantage and allows to ventilate our patients different even when neuromuscular block is given.

Today several versions of the OFA approach in Bruges exist. The OFA1 (CataKetaDrop mixture) works with Clonidine (Catapressan). When Dexdor becames available OFA 2 (Mulimix) was used with Dexdor (Dexmedetomidine) mixed in one syringe of 20 cc with Linisol (Lidocaine) and Ketalar (ketamine) for induction and maintenance.
OFA3 is the protocol with the use of a procaine infusion during surgery only. OFA4 is the protocol used for short procedures and children. OFA5 is the last protocol aimed at continuing some drugs postoperative in a low dose as described here:

The practical Brugge approach on dec 2014 is as follows (OFA5): How to do it?

1. Before Anaesthesia induction.
    a. Before induction place an iv line and start the infusion of procaine 0,1 % with **50 mg ketamine** (1cc Ketalar) and **5 gr Mgsulf** (2 amp of 2,5 gr in 5 cc) running at **1 ml/kg IBW/h** (Procaine 1 mg/kg/h) as a continuous infusion peri-operative. (You might be able to wait with the added drugs for post operative but this allows you to continue with the same setup per and post operative and forces you to reduce free fluid load. You might use lidocaine at 1 mg/kg IBW/h instead of procaine)
        i. Procaine 0,1 % is ready available on the market what simplifies its preparation. However the concentration of 0,1 % and the ideal dosis of 3 mg/Kg/h (same for lidocaine, max 6 mg/kg/h) would require an infusion of 3 ml/kg/h or 250 ml/h for a 75 kg person after a loading dose of 1,5 mg/kg. This high fluid load should be avoided except when hypovolemic and in the multimodal approach every drug can be used below its maximum dose according to safety and individual concerns. At the 6 mg/kg 500 ml can be given without any risk for a 75 kg person keeping it safer if the infusion line is flushed during the case. Procaine is safer than Lidocaine in its max dose that can be given. By running at 1 mg/kg/h extra loading of Lidocaine can be given. (See induction). Procaine 0,1 % = 1 mg/ml.
            1. Loading is also given (see induction with Lidocaine).
        ii. Mg sulf can be given at 10 mg/kg/h. To stay on the safe side 5 mg/kg/h is given (5 gr added instead of 10 gr MgSulf to infusion bag of 1 l).
            1. Loading is also given (see induction).
        iii. Ketamine is not needed for induction and not during anaesthesia. It reduces the analgesics post operative if used in a very low dose below hypnotic effect.
            1. It is however very important to be given before any opioids are given when required or when gradual changing from opioids to opioid free (opioid sparing) (to prevent hyperalgesia through its NMDa blockade. Ketamine is a lot

stronger than N2O and can be given further post operative as NMD blocker when Dipi or morphine is given as analgesics.

2. Therefore a dose of 50 mg in the infusion bag given over more than 10 hours is ideal.

iv. The infusion bag with ketamine, Mg and procaine is running at 1 ml/kg/h or the dose needed post operative. Due to a level below max it can be increased or a flush can be given without risk of overdose.

1. This guarantee stable delivery during and after surgery.

b. Before induction give **dexamethasone 10 mg**, (2 amp aacedexamine of 5mg in 1 cc) certainly for laparoscopy valuable.
   i. Dexamethasone reduces the pain level post operative only if given before surgery starts. The effect might be explained by its anti inflammatory effects on the surgical wound that will get less oedema and therefore less painful. The same effect is possible on the whole peritoneal mesothelium that is damaged by 100% CO2 or 21% O2 in laparotomy. Adding dexamethasone reduces peritoneal damage and keeps the peritoneal barrier intact explaining why CO2 resorption after one-hour laparoscopy does not rise dramatically. To improve further this protection 4 % O2 and/or 5 to 10 % N20 should be added to the CO2 gas, besides reducing the insufflator pressure, the length of the pneumoperitoneum and the bleeding inside the abdomen. You will have fewer problems in ventilation to get rid of the CO2, patients will have less pain post op and surgeons will have better wound healing without adhesions.
   ii. The reduction in pain level is most clear after laparoscopic surgery and therefore a must. After other surgery the effect is limited.

c. Before induction give **droperidol 1,25 mg.** (1 amp 1,25 mg in 2,5 cc)
   i. Droperidol in low dose reduces effectively the nausea and vomiting but is probably less required if OFA is used. Nevertheless inhalation and abdominal surgery still stimulates nausea and therefore a cheap and simple method, as droperidol should be kept as preventive therapy. In older patients it might also reduce the delirium postoperative already at a dose of 0,625 mg. At 0,625 mg no need to reduce the dose or to be afraid of sedation in older patients with renal insufficiency.

2. Anaesthesia induction
   a. Dexmedetomidine slow loading up of 0,5 to 1 ug/kg
      i. Make conc of 1 amp in 50 cc or 2 amp in 100 cc (4 ug/ml). Give **5 cc or 20 ug** first before intubation, proceed loading up depending on duration, age, etc. For a 2 h procedure in an 80 kg person gives **80 ug or 20 cc** over 15 minutes before incision.
      ii. Only if the operation is very long an extra infusion-pump with Dexmedetomidine is needed. If the operation is less than 1 hour, if the patient is old or has a weak Sympatico system a loading dose of 0,25/kg to 0,5 ug/kg is sufficient.

iii. The required amount varies between 0,5 and 1 ug/kg IBW. At 1 ug/kg the patient might not wake up immediately after surgery. Fast waking up depends also on the dose of inhalation and lidocaine or procaine used till the end. The patient will slowly wake up if an extra dose of lidocaine 1 mg/kg is given at the end of surgery. Be aware of the combination effects.

b. **Lidocaine 1 % 1 mg/kg** or **7 cc for 70 kg** person (because infusion with procaine is running reduce 1,5 mg/kg to 1 mg/kg or 1 cc/10 kg) it blocks the Sympatico stress.
   i. Lidocaine 1% = 10 mg /ml 1,0 mg/kg = 1,0 ml/10kg IBW.
c. **Propofol induction dose of 2,5 mg/kg**
   i. or **200 mg for a 80 kg** person
d. **Rocuronium dose if needed** for intubation 0,6 mg/kg IBW or 1,2 mg/kg RSI dose.
e. **Magnesium sulphate** (1 red amp = 5 cc or 2,5 gr; 1 blue amp = 10 cc or 0,5 gr) **40 mg/kg IBW or 2,5 gr** for a 65 kg person, loading after sleeping (warm feeling central effect if awake).
   i. It blocks the Sympatico stress and reduces blood pressure increase by dexmedetomidine. It accelerates (RSI), deepens and prolongs your NMB.

3. Anaesthesia Maintenance
   a. **Inhalation with 0,7 to 1 MAC**
      i. Measure BIS to adapt depth of hypnosis between 40 and 60 %.
   b. Or Propofol can be used at 10 mg/kg/h but sometimes this is even not enough as the opioid sparing effect is missing. Recovery time is longer and therefore no advantage in using Propofol over inhalation when 1 MAC is not needed.
   c. If surgery takes longer than 2 h give infusion of dexmedetomidine (4ug/ml) at 0,5 ug/kg/h and stop 30 minutes before end.
   d. Keep Procaine infusion with Mg, Ketamine running at 1 ml/kg/h. if insufficient vasodilation and reduction in cardiac output for controlled hypotension extra Mg can be given to total max of 10 to 15 mg/kg/h, but it is better to add beta blockers.
   e. Keep metoprolaat (Seloken 1 amp 5cc = 5 mg) and nicardipine (Rydene 1 amp 5cc = 5 mg) available if rapid decrease in heart rate or rapid drop in blood pressure is needed. Dexmedetomidine might not be loaded up sufficient and a further dose should be given but takes to long before its effect is seen.
4. Loading analgesics up before end of surgery.
   a. Ideal are moments when blood pressure is normal or high (use rapid loading of Paracetamol, diclofenac to reduce blood pressure)
   b. **Paracetamol.**
      i. TBW <50 kg: 1 gr
      ii. 50 kg <TBW < 100 kg: 2 gr
      iii. 100 kg < TBW: 3 gr
   c. **Diclofenac**
      i. 75 to 150 mg loading.
5. Extubation and post op analgesia.

a. If opioid sparing has been used, you might need now to give an additional dose of sufenta or dipi before awakening. Put the ventilator on pressure support mode and measure the respiratory frequency. If respiratory rate is more than 20 you might add 5 ug of sufenta (or 5 mg of piritramide (Dipidolor) or 5 mg morphine) without getting strong respiratory depression at awakening.
b. If opioid free has been used with dexmedetomidine, no opioid is needed in the first 30 minutes in most patients. Be sure to have given Paracetamol, non-steroidal antiflogistics, low dose ketamine, magnesium and Lidocaine or procaine. In case of allergy or side effects one of them can be omitted without increasing pain levels. By working multimodal not all drugs have to be given at maximum dose.
c. Continue with **Paracetamol 1 gr every 6h** and **diclofenac 75 mg every 12h**.
d. Continue the sympathetic block by loading up with clonidine 75 to 150 ug. You can also ad a very low dose of dexmedetomidine by giving 0,1 ug/kg/h by adding 100 ug dex to the infusion bag of 1000 ml. this is below the sedation dose and has analgetic properties. Howevr a continuous infusion of dexmedetomidine might require a followup difficult on a ward. Loading with clonidine is less effective, might give less controllable hypotension and bradycardia. Therefore load up with clonidine post operative only if SAP is above 100 mmHg and heart rate is above 70 beats per minute.
e. Keep giving a low dose of ketamine, procaine and Magnesium by letting the infusion bag run further at **1 ml/kg IBW/h**. If after 30 minutes patient has pain a low dose **morphine 3 to 5 mg** (or dipi 5 mg) can be given iv in the PACU. If patient remains too much sedated and surgery is not painful, stop procaine infusion with additives and continue with Paracetamol and non-steroidal analgesics.

Opioid free anaesthesia is something one has to learn as opioids are faster than alpha 2 agonists in blocking the Sympatico system and post operative bradycardia and hypotension are more common after alpha 2 agonists. Correct hypnotics given remain important and BIS or entropy can measure this. Clinical factors like heart rate and blood pressure or more specific tools like SSI, heart rate variability or Qnox can measure sympaticus block. NMT monitors should measure NMB.

J P Mulier MD PhD
Jan.mulier@azsintjan.be
www.publicationslist.org/jan.mulier
AzSintJan Brugge-Oostende
Belgium

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