



TriPom TOTM – The importance of pain management in perioperative outcomes including enhanced recovery pathways – Part One

MCQs –

1 Epidural analgesia has been shown to

- a) Attenuate the stress response to surgery
- b) Increase pituitary activation
- c) Increase risk of venous thromboembolism
- d) Reduce risk of post-operative ileus
- e) Reduce risk of myocardial infarction

2 Regarding paracetamol

- a) Is fully absorbed from the stomach
- b) Is an aniline derivative
- c) Is converted to phenacetin
- d) Is a useful anti-inflammatory agent
- e) Is excreted unmetabolized

3 Local anaesthetic agents (LA)

- a) duration of action is dependent on protein binding
- b) with low pKa have a faster onset of action
- c) potency is proportional to lipid solubility
- d) are all vasodilators
- e) increasing the dose increases the depth of local anaesthetic block



4 The adverse effects of NSAIDs on the kidney

- a) are reversible in normal kidneys
- b) are not dose related
- c) are mediated by inhibition of PGI₂ synthesis
- d) may cause acute interstitial nephritis
- e) are counteracted by the use of ACE inhibitors

5 Intravenous Lidocaine infusions

- a) Are safe when used in patients with severe renal dysfunction
- b) Have been shown to reduce the risk of post-op ileus in GI surgery
- c) Are best dosed according to ideal body weight
- d) Can be commenced following a bolus of IV lidocaine
- e) Have a solely analgesic effect

Key points:

- Analgesic methods should be considered early in the perioperative planning process
 - Analgesia should be considered on a patient- and procedure-specific basis
 - Optimal analgesia reduces length of hospital stay and improves patient satisfaction
 - Analgesia is a vital component of a complete enhanced recovery programme
 - Regional analgesic blocks are a crucial element of multimodal opioid sparing analgesia
 - "Alternative" therapies have limited evidence of efficacy but offer potential sources of analgesia in selected patients
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Introduction

Inadequate analgesia can result in an exaggerated stress-response, prolonged time to mobilisation, sleep deprivation, increased likelihood of side-effects from higher medication requirements and lower patient satisfaction (Fawcett, Mythen, & Scott, 2012). The need to effectively manage a patient's analgesia begins at an early stage of the



perioperative process and should form an integral part of the anaesthetic plan from the pre-assessment stage.

Positive outcomes after surgery represent not only the surgery itself but the entire perioperative management of each patient starting from the point of referral. It is well known the impact even single complications can have on surgical outcomes, the work of Khuri et. al. illustrated this vividly (Khuri, Henderson, DePalma, Mosca, Healey, & Kumbhani, 2005) (See fig. 1). The ever-growing body of evidence supporting or contesting all aspects of perioperative practice can muddy the water as to what will work best for individual patients. The approach to pain management is a vital part of the perioperative process and there are a number of factors which should influence how you approach pain management for each patient.

The underlying theme of this tutorial will be that of multi-modal, opioid-sparing analgesia. There is a growing trend towards reduced use, if not complete avoidance of, opioids owing to their well-known side-effect profile and increasing evidence of detrimental outcomes in cancer surgery. Of the primary elements that make up an enhanced recovery programme those relating to analgesia are specifically aimed at taking an opioid-sparing approach to anaesthesia (Fearon KC, 2005). This tutorial aims to explore the numerous analgesic modalities available to anaesthetists and their relative risks and benefits perioperatively.

Opioids

Opioid use remains widespread despite their well-known adverse effects including sedation, respiratory and cough depression, dysphoria, itching, post-operative nausea and vomiting (PONV), a delayed return to normal gastro-intestinal function and urinary retention. More recently there has been a focus on other issues surrounding perioperative opioid use such as tolerance, opioid-induced hyperalgesia and the immunosuppressive effects of opioids (Snyder & Greenberg, 2010) (Burns, Levins, & Buggy, 2016). There is no doubt that opioids are very effective analgesics and should

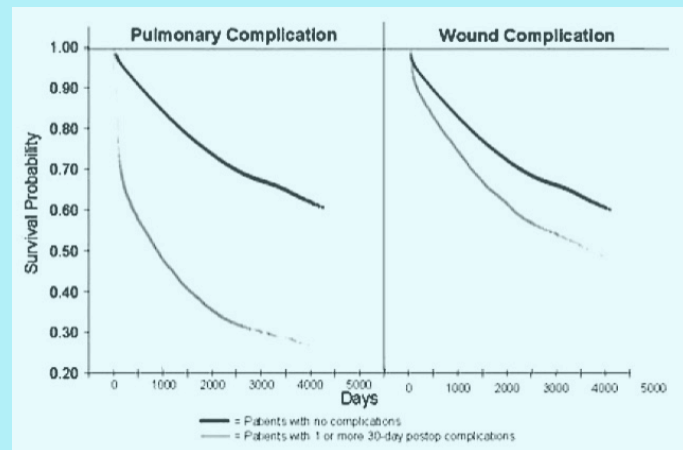


Figure 1 – Kaplan-Meier Curves showing effects of pulmonary or wound complications on overall survival. Khuri et. al. 2005



not be withheld from patients if other methods provide inadequate analgesia. Indeed, the use of opioids in the immediate post-operative period probably has little deleterious effect. The aim should not be total avoidance but conscientious use as part of a multi-modal approach (Kehlet & Dahl, 1993).

Naturally-occurring opioids (plant-derived amines) are produced from *P. somniferum*, the poppy. These are morphine, codeine, papaverine and thebaine. The semi-synthetic opioids include dihydrocodeine, diamorphine, buprenorphine, oxycodone, nalbuphine and naloxone. Finally, there are four classes of synthetic opioids (depending on how you classify opioids):

- morphinan derivatives (levorphanol, butorphanol)
- diphenylheptane derivatives (methadone, propoxyphene)
- benzomorphan derivatives (pentazocine, phenazocine)
- phenylpiperidine derivatives (pethidine, alfentanil, fentanyl, sufentanil and remifentanil)

The latter class the most widely used in anaesthetics. An alternative classification is by effect at opioid receptors (agonists, partial agonists, antagonists) (Pathan & Williams, 2012).

Morphine is considered the gold-standard opioid, with others such as codeine and tramadol frequently used. Codeine is renowned for constipation, making it less suitable in the context of enhanced recovery, and its variable metabolism should be considered in certain populations such as paediatrics. Tramadol has effects on opioid receptors alongside inhibition of serotonin and noradrenaline reuptake. This results in effective analgesia but with a side-effect profile many patients find intolerable, such as confusion or agitation. With a similar analgesic effect and mechanism of action Tapentadol has recently become available but remains under patent and thus less widely available. With only a weak serotonin reuptake inhibitory effect, requiring no metabolism to become effective and with no active metabolites Tapentadol has the potential to be considered as a useful adjunct to analgesia where previously tramadol would have been the drug of choice but, at present, no IM/IV preparation is available (Singh, Nag, Shetti, & Krishnaveni, 2013).

There remains an important role for opioids in patient-controlled analgesia (PCA) particularly in patients for whom regional analgesia may not be possible. Where possible you should consider which drug(s) you want to use in your PCA for your patient. Is morphine the right choice or would an alternative, such as fentanyl, be more appropriate? A 50:50 ketamine:morphine mix is currently gaining favour with a recent



systematic review suggesting improved pain scores (albeit just over a point reduction on the 0-10 scale), reduced morphine consumption and PONV with no increase in the incidence of respiratory or hallucinatory adverse events (Assouline, Tramer, Kreienbuhl, & Elia, 2016). The prolonged use of opioids should be avoided and increased doses may be required for patients already using regular opioids. The use of opioids is not restricted to systemic use but commonly used as adjuncts to epidural and intrathecal technique, a subject which will be returned to later in this tutorial.

Opioid-induced hyperalgesia is a topic currently under debate. This largely relates to perioperative remifentanyl and medium to long-term opioid use for chronic pain. It remains unclear as to the clinical significance of this effect however strategies such as the concurrent use of N-methyl-D-aspartate-antagonists (such as ketamine) are thought to attenuate this effect.

Epidural Analgesia

Where suitable epidural analgesia is regarded as the gold-standard in analgesia due not only to its excellent opioid-sparing effects but other described benefits too. These include improved post-operative pulmonary function (with a reduced incidence of pulmonary complications), attenuation of the stress response to surgery, with reduced sympathetic and pituitary activation resulting in reduced adverse metabolic effects (such as hyperglycaemia and protein breakdown), although with no effect on the cytokine-mediated inflammatory response. Epidural analgesia also reduces the incidence of ileus and PONV, thromboembolic events and blood loss with an earlier return to diet and some evidence to suggest a reduction in the rates of myocardial infarction, renal failure and mortality (Scott, et al., 2015).

In order to be effective several considerations must be taken in account:

- The level of insertion must be appropriate for the surgery taking place including likely positions of any surgical drains. Thoracic epidurals are more likely to be suitable for open abdominal and thoracic surgery both to block the necessary dermatomes for surgery and to reduce the incidence of leg weakness post-operatively.
- The choice of drugs to be infiltrated into the epidural space most often includes a local anaesthetic combined with an opioid such as fentanyl or diamorphine, however other adjuvants such as alpha-2-adrenoreceptor agonists (e.g. clonidine) or adrenaline have also been demonstrated to improve or hasten the analgesic effect but this is largely unnecessary in elective procedures.
- The post-operative environment must include staff trained in the effective management of epidurals to correctly titrate the rate of ongoing epidural infusion



and recognise and subsequently effectively treat known side-effects such as hypotension or motor block.

- Establishing the epidural is best undertaken early intraoperatively or in a post-operative care unit in order that it can be established the epidural is working effectively before returning a patient to a ward. Failed or inadequate blockade is commonplace and its early recognition is vital so that topping up with anaesthetic and/or opioid, re-siting or switching to alternative analgesia, such as morphine PCA, can be instituted.
- In the event of hypotension resulting from an epidural, excessive fluid administration should be avoided and the use of vasoactive drugs in a critical care environment are certainly more logical and may be preferable. Excessive fluid administration can lead to oedema (often with little effect on blood pressure) with the potential for detrimental effects on the cardiovascular and respiratory systems as well as any surgical anastomoses.
- Mobilisation may be impaired in the postoperative period due to leg weakness, hypotension and attachment to drips etc.

There also remain a number of conditions in which an epidural may not be suitable for patients. Those with known a known coagulopathy or concurrently receiving coagulation-modifying drugs should be considered on an individual basis and guidelines are widely available detailing the coagulation states when epidurals or other neuraxial interventions should be avoided and the medications which must be stopped, alongside when to stop them, prior to any neuraxial procedure (Ireland, 2013). Other conditions such as patient refusal, concurrent septicaemia (increasing the risk of epidural abscess), and cardiac conditions in which patients are dependent on a higher systemic vascular resistance (i.e. severe aortic stenosis) are also contraindications.

More rare complications of epidural insertion can have particularly devastating effect. Vertebral canal and spinal cord compression can be a result of epidural haematoma or abscess with symptoms mimicking the effect of an effective epidural, namely leg weakness, alongside back pain. If cessation of local anaesthetic infusion fails to resolve symptoms immediate imaging and expert advice must be sought. A more common occurrence is accidental dural puncture which can lead to severe headache with the rare possibility of more serious complications such as subdural haematoma. NAP-3 gives an excellent summary of known complications of neuraxial and regional blockade (Anaesthetists, Third National Audit Project of the Royal College of Anaesthetists (NAP3): Major complications of central neuraxial block, 2009).



Spinal anaesthesia

Intrathecal analgesia, although regarded as safer than epidural, may be unsuitable for major open surgery due to its limited duration of action offering little in the way of ongoing post-operative analgesia. The spinal may be more beneficial than epidural if the aims are fast-acting, short-duration, highly effective analgesia with little pulmonary effect alongside many of the epidural benefits such as opioid-sparing, reduced stress-response and reduced blood loss. In fact, a spinal may be superior to epidurals in certain outcomes such as opioid-sparing, PONV and return of GI function (Virlos, Clements, Beynon, Ratnalikar, & Khot, 2010).

Hypotension is the main fear when using spinals and it can occur rapidly and profoundly. The elderly, underfilled and patients with cardiac valvular disease are most at risk. These patients are at risk of receiving inappropriate volumes of intravenous fluid leading to an increased risk of oedema.

Incidents of awareness are often attributed to cases relying on regional analgesia and sedation whereby patients are not aware that they may be aware. A gentle explanation of the intended effects of sedation is pertinent pre-operatively on these occasions (Anaesthetists, Major complications of airway management in the United Kingdom, 2011).

Controversy surrounds what drugs are most suitable when performing a spinal. Intrathecal diamorphine is unlicensed but widely used. There is a lack of evidence that other additives, such as clonidine, confer any significant post-operative outcomes and they may, quite possibly, increase the risk of adverse effects such as drowsiness.

Regional Blockade

This is a very large topic in itself and would require its own tutorial to fully explore the many techniques available. There are many excellent resources available on this topic, for example NYSORA (www.nysora.com) and LSORA (www.lsora.org) which are highly recommended.

Regional blocks are generally considered safer than spinals or epidurals but generally require higher doses of local anaesthetic which, depending on the location of the block (intercostal being most risky), can increase the risk of local anaesthetic toxicity.

The use of wound catheters go somewhat against the principles of enhanced recovery but no more so than an epidural catheter. Similar to epidurals, however, they are at risk of malposition or misplacement and infection although evidence is sparse for the latter. Evidence varies as to their efficacy with studies showing either equivalent analgesia to



an epidural (Bertoglio, Fabiani, Negri, & al., 2012) but others refuting this (Jouve, Bazin, Petit, & al., 2013).

Systemic Analgesia

Paracetamol (acetaminophen), an aniline derivative, remains popular offering effective, non-opioid analgesia with an excellent safety record when used appropriately. The intravenous preparation allows administration in patients unable to take enteral medication thus offering a further non-opioid analgesic. Caution must be taken in patients with a background of hepatic or renal dysfunction owing to potential harm from active metabolites adult patients weighing less than 50kg must be appropriately dosed.

Non-steroidal anti-inflammatory drugs (NSAIDs) have an important role in analgesia but evidence varies between preparations as to their safety profile regarding bleeding, cardiovascular complications, renal failure, wound healing and anastomotic leakage after colonic surgery. In euvoelaemic patients it is unlikely that they would be at an increased risk of renal injury (Myles & Power, 1998). Both selective (e.g. parecoxib, celecoxib) and non-selective (e.g. diclofenac) are thought to increase the risk of anastomotic leak but non-selective more so (Gorissen, et al., 2012).

Gabapentinoids have been shown to reduce post-operative pain, opioid consumption and PONV although can cause sedation, visual disturbances and dizziness with the more recently developed pregabalin having a better pharmacological profile than gabapentin. The optimal dose of pregabalin remains unresolved with 150-300mg pre-operatively being most commonly used although higher doses confer a higher rate of adverse effects (Eipe, et al., 2016). These drugs may also help to prevent the onset of chronic post-surgical pain. Because of their sedative effects caution should be used in the context of enhanced recovery and evidence is lacking for their use in areas such as open abdominal surgery.

NMDA antagonists (ketamine and magnesium) are useful adjuncts in acute pain with effects on acute tolerance and hyperalgesia with central desensitisation. Optimal dose and duration of using ketamine infusions intra-operatively remains unclear but even low doses reduce morphine consumption with a low adverse-effect profile and demonstrable anti-inflammatory response. Ketamine may be useful for patients who are opioid-tolerant and for reducing chronic pain but there remains a lack of procedure-related evidence for its use at present. Magnesium has been shown to improve post-operative pain scores and reduce opioid consumption (De Oliveira, Castro-Alves, Khan, & McCarthy, 2013) but prolongs neuromuscular blockade.



Alpha-2-agonists (clonidine and dexmedetomidine) have an analgesic effect through reduction of sympathetic outflow and noradrenaline release within the central and peripheral nervous systems interrupting pain pathways, including the release of the substance P. Clonidine is often used as part of a nerve block or intrathecal preparation for its analgesic effect, however, its adverse effect profile (sedation, hypotension, bradycardias) make it otherwise less popular, particularly in enhanced recovery. Dexmedetomidine is also popular in bariatric practice and patients with obstructive sleep apnoea conferring an analgesic benefit alongside reduced PONV and faster times to mobilisation.

Glucocorticoids can have an opioid-sparing effect alongside reducing PONV, length of stay and modifying the stress response to surgery. The use of glucocorticoids is currently controversial in surgery for malignant disease due to conflicting evidence regarding disease recurrence and there is insufficient evidence at present to suggest glucocorticoids should be omitted during cancer surgery. In orthopaedic surgery, there has been considerable success with the use of high-dose methyl-prednisolone, with concerns of hyperglycaemia and wound infections not being a major issue.

Lidocaine Infusions: Intravenous or intraperitoneal lidocaine infusions have been around for a while and seem to come-and-go in favour. Currently they are gaining in popularity but not without controversy. In theory, they are excellent methods of analgesia. They have been shown to offer analgesia equivalent to an epidural whilst being safer, anti-inflammatory and anti-bacterial with possible inherent immunomodulatory effects improving cancer outcomes. They can promote cell-mediated immunity and reduce cancer spread and metastatic mechanisms (Eipe, Gupta, & Penning, Intravenous lidocaine for acute pain: an evidence-based clinical update, 2016) (Kahokehr, Sammour, Shoshtari, Taylor, & Hill, 2011). A major benefit from intravenous lidocaine (IVL) is on the GI tract with considerable evidence to show reduced risk of post-operative ileus. Several specialities also benefit from reduced length of hospital stay (most notably GI and urological procedures) when compared to systemic opioids.

The caveat to the earlier mention of analgesic benefit is that not all studies agree on how good IVL can be for analgesia. A recent systematic review showed such variation in results between studies that it was difficult to conclude that, other than for open or laparoscopic abdominal surgery, IVL offers significantly improved analgesia, particularly beyond the first 36 hours. One problem is that no-one can agree on how best to deliver lidocaine. Most studies give a first dose or start the infusion before knife-to-skin but the question of when is best to cease an infusion remains unanswered.

The adverse effect profile is, fortunately, very small with most studies only reporting minor side-effects such as light-headedness or transient arrhythmias. There are,



however, several case reports of more serious events, including death. These have a theme of incorrect administration (bags of lidocaine left open to run when assumed to be colloid, etc.) or poor patient choice. Concurrent illness such as sepsis, where a patient may be profoundly acidotic, may render IVL inappropriate due to reduced seizure threshold. At present continuous cardiac monitoring is recommended for patients receiving IVL infusions thus at least a level one bed would be needed post-operatively or prolonged stay in recovery/post-anaesthetic care unit until the infusion is stopped. This puts an increased burden on resources in isolation but most patients for whom IVL would offer a benefit are likely to require a higher level of care post-operatively for procedure-specific reasons in any case.

Others: TENS, hypnosis, acupuncture etc. do not currently figure in any enhanced recovery protocols, but who's to say what is around the corner? Many studies suggest they may be no better than placebo, however, placebos themselves have been shown to improve outcomes such as pain scores and patient satisfaction. These techniques are great examples of when patient-specific considerations are particularly important. Patients have an ever-increasing depot of information available to them, admittedly of varying accuracy to put it mildly. Some can become especially fixated upon the potential efficacy of certain methods and may convince themselves that they will work better than those clinically proven to be effective. This strength of conviction should not be ignored, within reason. TENS machines are widely used in maternity services by patients driven by anecdotal as much as clinical evidence as to their efficacy. Their role in acute pain beyond obstetrics is very limited but they give a good example of a means of analgesia which patients themselves can instigate allowing them greater autonomy over their care. In more regular use perioperatively the PCA works on a similar principle beyond the innate pharmacological actions of the drugs in the syringe. The element of control patients have over their own care can help improve their sense of managing their own pain effectively.

In Summary

Analgesia is a broad topic with an ever-increasing arsenal of drugs/methods to help ensure our patients are comfortable perioperatively. The earlier we are able to plan our anaesthetic, not least the analgesia, to sooner we can allow our patients to become a part of the process. Be this through simple education methods such as leaflets or directing them to suitable websites or through pre-operative discussions detailing the rationale behind a plan and what patients themselves can do to improve their own experience. Procedure-specific analgesia means a multi-disciplinary approach with discussions with surgeons as to the scope and extent of the planned procedure. This will



help to answer questions such as will a spinal suffice or will the patient have longer-term analgesia requirements necessitating an epidural? Post-operatively the environment in which they will be cared for must be suitable for the task and, in the least, be able to adequately assess pain, have means by which to treat or seek appropriate advice at all hours and be able to encourage patients to deep breath and cough at regular intervals. If this is something a patient cannot do satisfactorily then urgent help must be sought.

Patients must also be comfortable enough to mobilize early, another vital element of enhanced recovery. A working epidural may do wonders for alleviating pain but if confining a patient to the bed the rate of any ongoing epidural infusion may need to be reduced.

An excellent resource is available on the PROSPECT group's website (www.postoppain.org) with evidence-based guidelines for a number of common surgical procedures. This procedure-specific approach details which interventions have the current backing of a considerable body of evidence but leaves room for individual variation dependent upon your patient's individual needs.

MCQ Answers

- 1 TFFT
- 2 FTFF
- 3 TTTT
- 4 TFTT
- 5 FTTF

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