Acute Pain Update

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When I was asked to talk about "Acute Pain: An Update", I experienced first hand what psychologists call "the distant elephant phenomenon". This phenomenon refers to situations where something in the distance appears small, non-threatening and quite manageable. However, the closer you move to it (the elephant), the bigger and less manageable it becomes until you are really up close, stare it in the eye and just realise how an intimidating beast it is.

Why is acute pain such an intimidating topic? I believe the reasons are many. Firstly, the definition of pain is very subjective. Secondly, pain may have an emotional component and the pain experience may not be the same for any two patients. Our ability to measure pain is not particularly sophisticated and this is especially true when patients use our "tools" for pain assessment to verbalise anxiety and distress in addition to their pain. Add to this the fact that the literature on acute pain medicine is often conflicting, the studies suffer from significant heterogeneity and even the findings of good studies may not be implementable in your institution for a variety of reasons and "voilà": You have a distant elephant! It is not possible to offer an exhaustive update on the literature concerning acute pain. Instead I wanted to focus on some topics that seem relevant to our daily practise. Our understanding of these topics is evolving and in discussing this, the difficulties in navigating the literature will be highlighted.

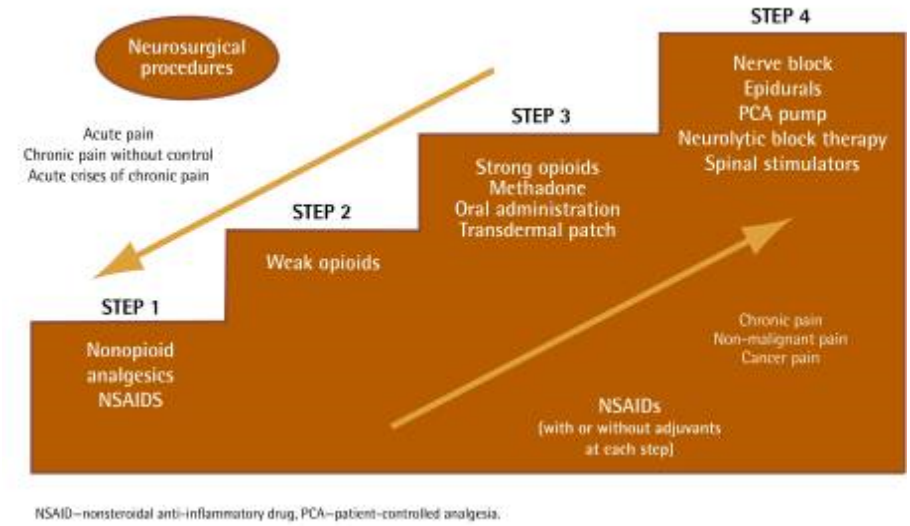
These topics are:

1. Has the basic framework for pain management changed?
2. Cancer and the analgesics we use.
3. Pre-emptive and preventative analgesia and treatment of established pain.
4. Ketamine is good for pain! Right?
5. Methadone. Can you teach an old drug new tricks?
6. Other "Pain stuff".

Has the basic framework for pain management changed?

The World Health Organization (WHO) developed the analgesic ladder as a guide for managing cancer pain in 1986 and revised it in 1997 with the addition of "adjuvants". The key principles were "step-up" analgesia as required or "step-down" analgesia as stronger drugs were no longer needed and it advocated "by the clock" administration of analgesics rather than "on demand" dispensing. The "right drug; at the right dose; at the right time" was inexpensive and 70-80% effective. [1, 2] It was widely adopted across the world with many subsequent modifications that have seen its implementation in both acute and chronic pain. In 2010 one such a modification of the analgesic ladder was published in the Canadian Family Physician. [2]

Figure 2. New adaptation of the analgesic ladder



(Reproduced with permission. Grisell Vargas-Schaffer. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010 Jun; 56(6): 514–517)

Combined with the key principles underpinning the original analgesic ladder, it is still highly relevant and a useful frame for the management of acute pain. As anaesthetists we typically start at "step 4" with a sophisticated pain management modality and then "step-down" as patients' needs changes post-operatively. Similarly we "step-up" analgesia when pain is poorly controlled.

Cancer and the analgesics we use

Opioids

One of our roles as anaesthetists is to facilitate surgery for our patients but our involvement in patients' journeys are, relatively speaking, short lived. Is it possible that our actions and drugs could have an effect on the long term outcomes that were traditionally thought to be primarily determined by the scalpel of a surgeon and the drugs of a physician? This question dates back to as far as 1962 and in the last 10 years questions on the longer term effects of commonly used agents, especially opioids and their potential role in cancer recurrence, have intensified. [3]

Opioids have been shown to affect tumour cell proliferation and tumour apoptosis. Opioids modulate angiogenesis and processes involved in tumour growth and invasion through direct and indirect mechanisms such as alteration of the inflammatory micro-environment. Opioids are immunosuppressive with good evidence pointing to inhibition of Natural Killer (NK) cells in particular. This is important as NK cells are implicated in cancer protection by "mopping up" rogue disseminating cancer cells. [4, 5]

Complicating matters is the fact that not only morphine, but pain can also strongly inhibit NK cells and as a result, poorly controlled pain may influence cancer spread and recurrence. It is interesting that endogenous opioids seem to improve NK cell activity which likely confers protection against cancer cell dissemination. [4]

Retrospective studies have shown reduced cancer recurrence after regional anaesthesia and reduced opioid use in prostate, breast and ovarian adenoma carcinoma but it is not clear whether the benefit arises from reduced opioid use or protection through a mechanism conferred by regional anaesthesia. [6, 7, 8] Interestingly, regional anaesthesia and reduced morphine use does not seem to confer the same protection in colonic cancer [5] or hepatocellular cancer where patients receiving epidural analgesia with morphine had higher cancer recurrence rates and higher mortality than patients receiving intravenous fentanyl. [9]

In vitro studies showed enhanced cancer cell proliferation with low doses of morphine but with high doses or prolonged exposure morphine suppressed cancer cell proliferation and caused apoptosis. [10] Remifentanil and fentanyl did not seem to affect cancer cell growth at any dose and tramadol suppressed the immune system less than morphine and suppression was only temporary. [10, 11]

Nonsteroidal anti-inflamatory drugs (NSAID)

A number of human and animal studies showed cyclooxygenase-2 (COX-2) overexpression was associated with cancer recurrence and was an unfavourable prognostic factor. [12, 13]

Treatment with a NSAID reduced cancer recurrence rates and time to recurrence in obese patients with breast cancer. [14] However; treatment with celecoxib 200mg twice daily for 12 months showed no benefit in bladder tumour recurrence. [15] Muddying the waters further were studies showing that COX-2 expression in proliferative breast cancer resulted in poorer survival outcomes but that COX-2 expression was protective, and considered a favourable prognostic factor, in non-proliferative breast cancer leading to better outcomes. [16]

Ketamine has anti-inflammatory properties through NMDA antagonism, reducing COX-2 and Il-6 expression, with animal studies showing anti-tumour effects in mice. [17] Evidence exists that ketamine reduces opioid consumption; even in opioid tolerant patients [18]. Human studies are still lacking.

There is almost a universal call to perform larger multi-centred studies to examine the relationship between cancer recurrence, opioids and other drugs. I fear that larger studies may prove counterproductive as the evidence suggests finer nuances in the relationship between cancer cells, the immune system and the drugs we use. This may be a case where bigger is not better as smaller, more specific studies could prevent these finer important nuances being lost in larger data sets.

In summary:

- There is a growing body of evidence that suggests that morphine (in particular) may be bad for you if you have cancer.
- COX-2 expression is generally seen as an unfavourable prognostic factor.
- Non-steroidal anti-inflammatories may confer some protection through COX-2 inhibition but evidence suggests that this may be specific to the cancer type or even subtype.
- The type of NSAID used to inhibit COX-2 does not appear to be important.
- There is established literature that pain and surgical stress suppress the immune system and diminish the body's natural defences against cancer.

A suggested practical approach from the available literature may include:

- Control acute pain and the surgical stress response with adequate anaesthesia, multimodal analgesia (including NSAIDS) and regional anaesthesia or a combination of these tailored to the needs and comorbidities of the patient.
- With respect to the use of morphine and opioids in cancer surgery a recent consensus statement from the BJA Workshop on Cancer and Anaesthesia found no conclusive evidence to change clinical practice.
- Keep current with the literature and be prepared to change practice as ongoing investigation and studies shape our understanding.

Pre-emptive and preventative analgesia and the treatment of established pain

Preventative analgesia is defined as an analgesic intervention that has an effect on postoperative pain and/or analgesic consumption that exceeds the expected duration of action of the drug. Pre-emptive analgesia refers to the timing of an intervention being performed pre-incisional. [19]

Paracetamol

The safety profile, ease of administration and cost effectiveness of paracetamol has seen it become a popular premedication that is well established in anaesthetic practice. Does the timing of paracetamol administration matter? In a recent study comparing pre-emptive intravenous (IV) paracetamol with

intra-operative paracetamol in functional endoscopic sinus surgery (FESS), time to first analgesic requirement was longer and rescue analgesic consumption and post-operative VAS pain scores were lower in the pre-emptive group up to 24 hours after surgery. [20]

Gabapentin and Pregabalin

Gabapentin is an interesting drug. It was originally approved in December 1993 by the FDA for use as an adjuvant medication to control partial seizures in adults. Our understanding of its mechanism of action continues to evolve and in addition to an impressive list of "off-label" uses [21] it seems to have established itself in anaesthetic and pain management practice.

A number of studies have been published with respects to gabapentin and pregabalin's use as a pre-emptive or preventative drug and acute pain adjunct. Results were conflicting with two studies showing the efficacy of single doses of 600mg gabapentin and 150mg pregabalin for increasing the duration of postoperative analgesia, reducing the requirement for rescue analgesia, decreasing postoperative pain scores and opioid use [22, 23] but gabapentin 600mg as premedication had no opioid sparing effect compared to placebo for abdominal hysterectomy in another study. [24] Gabapentin 900mg or 1200 mg, but not 600mg, administered either pre- or post-incision, was found to be effective in pain management following lumbar laminectomy [25] and gabapentin and pregabalin was effective in preventing chronic pain at one year following lumbar discectomy. [26]

A recent review (2014) on non-opioid analgesic use for pain prophylaxis and established pain helps to clarify the efficacy of individual drugs in these areas. [27]

Paracetamol (oral and IV) was opioid sparing (up to 20%) when given as pain prophylaxis and oral paracetamol had a number needed to treat (NNT) of 3.6 (95% CI 3.4, 4.0) for "established" pain. [27]

The evidence for NSAIDs was convincing for the treatment of "established" pain with a NNT of 2.5 (2.4, 2.6) and 2.7 (2.3, 3.3) for a single 400mg or 500mg dose of ibuprofen or naproxen respectively. NSAIDs were also opioid sparing leading to reduced opioid related side effects and complications, especially sedation and post operative nausea and vomiting (PONV). [27]

COX-2 selective drugs had comparable NNT to other NSAIDs for the treatment of "established" pain and also had an opioid sparing effect. However, this did not seem to translate to reduced opioid related adverse effects. [27]

A meta-analysis places the NNT for gabapentin (200-500mg) at 11 for the treatment of acute pain. Its opioid sparing effect (13-32mg morphine/24hrs) was consistent and clinically significant, resulting in reduced urinary retention (NNT=7) and vomiting (NNT=6), but not nausea. [27]

Pregabalin was opioid sparing 24 hrs after surgery at all doses <75mg – 300mg but no differences were identified on acute pain outcomes between single and multi-dose regimes. The review concluded that pregabalin compared to placebo improved post-operative analgesia at the expense of sedation and visual disturbance. [41]

The authors concluded that the numbers needed to treat should be interpreted with care, as the definition of NNT suffers from the potential of not including substantial pain relief in major surgery that just does not amount to a 50% reduction on the visual analogue scale (VAS).
In summary:

- It would appear that paracetamol and NSAIDs (including COX-2 selective drugs) are useful in the context of treating acute established pain.
- Both NSAIDs and paracetamol used for "pain prophylaxis" are opioid sparing and reduce opioid related side effects. The opioid sparing effect of COX-2 selective inhibitors does not appear to reduce opioid related side effects.
- The evidence for gabapentin's role in treating acute pain is less established and it would appear that doses less than 600mg are not very effective. Gabapentin is opioid sparing but sedation is potentially problematic.

- Is appears that pregabalin may be a useful adjunct in treating acute post surgical pain, but at the expense of sedation and visual disturbances. There appears to be no difference in acute pain outcomes between single and multi-dose regimens.

Data on combinations of the drugs discussed previously is scarce. [27]

Ketamine is good for pain! Right?

The evidence published in the last six years for the use of ketamine in acute pain and the prevention of chronic pain is conflicting.

There was no difference in early and late postoperative pain and morphine consumption with ketamine administered at doses of 0.25, 0.5, and 1 mg/kg in women undergoing Caesarean delivery under general anaesthesia [28] and diclofenac 100mg suppositories were more effective and had fewer troublesome side effects that 0.15mg/kg ketamine for elective gynaecological laparoscopy. [29] A number of studies have failed to show evidence for the use of ketamine to prevent chronic pain or for its use as an adjunct to acute pain management in the context of thoracotomy surgery. [30, 31, 32]

In contrast, a single dose of 15mg ketamine in combination with hydromorphone provided substantial analgesia for severe acute pain (NRS > 9) in the emergency department [33] and low dose ketamine (0.5mg/kg bolus followed by 0.1mg/kg infusion for 24hrs) significantly reduced post-op pain and opioid consumption in limb fracture surgery. [34] The pre-induction administration of intramuscular ketamine between 25-40mg showed significantly lower 48hr pain scores and approximately 35% less morphine use, again in the context of lower limb fracture surgery. [35]

An important study compared the effect of ketamine (0.3mg/kg bolus plus an infusion of 0.05mg/kg/hr till the end of surgery) versus gabapentin (1200mg pre induction with a bolus and infusion of saline) on acute pain, opioid consumption and the prevention of chronic pain. Gabapentin and ketamine were similar in improving early acute pain and both gabapentin and ketamine reduced morphine consumption (35% and 42% respectively). At six months post surgery gabapentin, but not ketamine, seemed to have reduced chronic pain after hysterectomy. [36]

In hip arthroplasty Ketamine decreased morphine consumption at 24h and at day 30, patients receiving ketamine were more mobile needing less assistance. At day 180 patients receiving Ketamine had clinically and statistically significant less pain (8% vs 21%; p=0.036). [37]
In summary:

- It would appear that Ketamine can be a useful adjunct in controlling acute pain especially in limb fracture surgery.
- Ketamine is opioid sparing.
- The evidence for Ketamine protecting against the development of chronic pain is conflicting.
- It would also seem that in thoracic surgery its use as an adjunct to acute pain management is doubtful.

Methadone. Can you teach an old drug new tricks?

The literature on the use of methadone in acute pain is surprisingly scant. A single dose of methadone (0.2mg/kg) for multilevel complex thoracolumbar surgery reduced postoperative opioid requirement by approximately 50% (25 mg morphine equivalents) at 48 and 72 hours compared to sufentanil (63mg morphine equivalents). In addition, pain scores were lower by approximately 50% in the methadone group at 48 hours after surgery and the incidence of side effects was comparable in both groups. [38]
I use IV methadone regularly when I am concerned about post-operative pain or where long lasting analgesia is required. Conceptually I think of methadone 0.1-0.2mg/kg IV as an easily titratable, "long acting morphine" with a hint of ketamine when used in theatre or recovery. It has complex pharmacology when given orally, with repeated dosing or with long term use and therefore; in the context of acute post surgical pain, I tend to avoid it in the ward in favour of fentanyl or morphine patient controlled analgesia (PCA) or oral sevredol or oxycodone. Anecdotally, I have found methadone useful as a "rescue analgesic" in the recovery room on a number of occasions.

Other "pain stuff"

1. Cebranopadol

Cebranopadol is a first in its class opioid and nociceptin/orphanin FQ receptor agonist (NOP). It is unique in being a single molecule with agonistic properties at MOP and NOP receptors with a 3- to 38-fold lower affinity for KOP in humans and the rat and ~20-fold lower affinity for DOP in humans.

Phase II trials show promise for its use in acute nociceptive and neuropathic pain as well as chronic pain and Phase III trials are underway.

Favourable pharmacology appears to include a time to peak effect of 20min when administered IV and 90min for oral administration with anti-nociceptive effect evident at 7 hours. Tolerance to equi-analgesic doses of cebranopadol developed at day 26 compared to morphine at day 11. [39]

2. Tramadol use in the immediate post-operative period. How good is it really?

A recent systematic review and meta-analysis (2015) suggest that combining tramadol with morphine in the immediate postoperative period appears to be limited to slightly lower levels of morphine use after surgery compared to placebo or non-opioid analgesics. Pain intensity at rest at 24 hours was no better and there was no_detectable benefit on the incidence of opioid-related adverse effects. [40]

3. Opioid-induced hyperalgesia (OIH). Is it real?

In a review published in 2009 it was concluded that there was not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers. [42] A more recent review and meta-analysis suggested that the clinical impact of remifentanil-induced hyperalgesia in the immediate postoperative period appeared to be limited to a slight increase in pain intensity at rest persisting for 24 h. It also showed a moderate increase in morphine use without influencing opioid-related side-effects. [43]

In summary: It would appear to be a real phenomenon mostly associated with high dose remifentanil. It does not appear to be clinically problematic.

References

1. http://www.who.int/cancer/palliative/painladder
2. Grisell Vargas-Schaffer. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010 Jun; 56(6): 514–517
3. Nomura Y; Kawaraguchi Y; Sugimoto H; Furuya H; Kawaguchi M. Effects of morphine and fentanyl on 5-fluorouracil sensitivity in human colon cancer HCT116 cells. Journal Of Anesthesia [J Anesth] 2014 Apr; Vol. 28 (2), pp. 298-301
4. Young MJ; Alston TA. Does anesthetic technique influence cancer? Journal Of Clinical Anesthesia [J Clin Anesth], 2012 Feb; Vol. 24 (1), pp. 1-2
5. Afsharimani B; Cabot P; Parat MO. Morphine and tumor growth and metastasis. Cancer Metastasis Reviews [Cancer Metastasis Rev] 2011 Jun; Vol. 30 (2), pp. 225-38]
6. Biki B, Mascha E, Moriarty DC, Fitzpatrick JM, Sessler DI, Buggy DJ. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. Anesthesiology 2008;109(2):180–7.
7. Exadaktylos AK, Buggy DJ, Moriarty DC, Mascha E, Sessler DI. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? Anesthesiology. 2006;105(4):660–4.
8. Lin L, Liu C, Tan H, Ouyang H, Zhang Y, Zeng W. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: a retrospective analysis. Br J Anaesth. 2011;106(6):814–22.
9. Cao L; Chang Y; Lin W; Zhou J; Tan H; Yuang Y; Zeng W. Long term survival after resection of hepatocellular carcinoma: a potential risk associated with the choice of post operative analgesia. Anesthesia and Analgesia [Anesth Analg] 2014 Jun; Vol. 118(6):1309-16.

10. Nomura Y; Kawaraguchi Y; Sugimoto H; Furuya H; Kawaguchi M. Effects of morphine and fentanyl on 5-fluorouracil sensitivity in human colon cancer HCT116 cells. Journal Of Anesthesia [J Anesth] 2014 Apr; Vol. 28 (2), pp. 298-301
11. Sacerdote P, Bianchi M, Gaspani L et al. The effects of tramadol and morphine on immune responses and pain after surgery in cancer patients. Anesth Analg 2000; 90: 1411–4
12. Kim, Hee Sung; Moon, Hyeong-Gon; Han, Wonshik; Yom, Cha Kyung; Kim, Woo Ho; Kim, Jun Ho; Noh, Dong-Young. COX2 overexpression is a prognostic marker for Stage III breast cancer. Breast Cancer Research and Treatment. Feb 15, 2012, Vol. 132 (1):51-9
13. Yoshikawa R; Fujiwara Y; Koishi K; Kojima S; Matsumoto T; Yanagi H; Yamamura T; Hashimoto-Tamaoki T; Nishigami T; Tsujimura T. Cyclooxygenase-2 expression after preoperative chemoradiotherapy correlates with more frequent esophageal cancer recurrence.World Journal Of Gastroenterology: WJG [World J Gastroenterol] 2007 Apr 28; Vol. 13 (16), pp. 2283-8
14. Bowers LW; Maximo IX; Brenner AJ; Beeram M; Hursting SD; Price RS; Tekmal RR; Jolly CA; deGraffenried LA. NSAID use reduces breast cancer recurrence in overweight and obese women: role of prostaglandin-aromatase interactions. Cancer Research [Cancer Res] 2014 Aug 15; Vol. 74 (16):4446-57
15. Sabichi AL; Lee JJ; Grossman HB; Liu S; Richmond E; Czerniak BA; De la Cerda J; Eagle C; Viner JL; Palmer JL; Lerner SP. A randomized controlled trial of celecoxib to prevent recurrence of nonmuscle-invasive bladder cancer. Cancer. Prevention Research (Philadelphia, Pa.) [Cancer Prev Res (Phila)] 2011 Oct; Vol. 4 (10):1580-9
16. Park BW; Park S; Park HS; Koo JS; Yang WI; Lee, JS; Hwang, H; Kim, SII; Lee, KS. Cyclooxygenase-2 expression in proliferative Ki-67-positive breast cancers is associated with poor outcomes. Breast Cancer Research and Treatment. June 1, 2012, Vol. 133 Issue 2, p741, 11
17. Snyder GL, Greenberg S. Effect of anaesthetic technique and other peri-operative factors on cancer recurrence. BJA 105 (2):106-115 (2010)
18. Loftus RW; Yeager MP; Clark JA; Brown JR; Abdu WA; Sengupta DK; Beach ML. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology [Anesthesiology] 2010 Sep; Vol. 113 (3):639-46
19. Macintyre PE; Scott DA; Schug SA; Visser EJ; Walker SM. Acute Pain Management Scientific Evidence 2010 3rd Edition. ("Blue Book")
20. Koteswara CM. A Study on Pre-Emptive Analgesic Effect of Intravenous Paracetamol in Functional Endoscopic Sinus Surgeries (FESSs): A Randomized, Double-Blinded Clinical Study. D S, Journal Of Clinical And Diagnostic Research: JCDR [J Clin Diagn Res] 2014 Jan; Vol. 8 (1): 108-11
21. Mack A. Examination of the evidence for off-label use of gabapentin. J Manag Care Pharm 2003 Vol. 9 (6): 559–68.
22. Bafna U; Rajarajeshwaran K; Khandelwal M; Verma AP. A comparison of effect of preemptive use of oral gabapentin and pregabalin for acute post-operative pain after surgery under spinal anesthesia. Journal Of Anaesthesiology, Clinical Pharmacology [J Anaesthesiol Clin Pharmacol] 2014 Jul; Vol. 30 (3): 373-7
23. Pandey CK; Karna ST; Tandon M; Pandey VK; Singh A. Comparative evaluation of prophylactic use of pregabalin, gabapentin and diclofenac sodium for prevention of succinylcholine-induced myalgia: a randomized, double-blinded study. Journal Of Postgraduate Medicine [J Postgrad Med], 2014 Jan-Mar; Vol. 60 (1): 16-20
24. Joseph TT; Krishna HM; Kamath S. Premedication with gabapentin, alprazolam or a placebo for abdominal hysterectomy: Effect on pre-operative anxiety, post-operative pain and morphine consumption. Indian Journal Of Anaesthesia [Indian J Anaesth], 2014 Nov-Dec; Vol. 58 (6): 693-9
25. Khan ZH; Rahimi M; Makarem J; Khan RH. Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: a randomized study. Acta Anaesthesiologica Scandinavica [Acta Anaesthesiol Scand], 2011 Mar; Vol.55 (3): 306-12
26. Dolgun H; Turkoglu E; Kertmen H; Gurer B; Yilmaz ER; Comoglu SS; Sekerci Z. Gabapentin versus pregabalin in relieving early post-surgical neuropathic pain in patients after lumbar disc herniation surgery: a prospective clinical trial. Neurological Research [Neurol Res], 2014 Dec; Vol. 36 (12):1080-5

27. Dahl JB; Nielsen RV; Wetterslev J; Nikolajsen L; Hamunen K; Kontinen VK; Hansen MS; Kjer JJ; Mathiesen O. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. Scandinavian Postoperative Pain Alliance (ScaPAlli), Acta Anaesthesiologica Scandinavica [Acta Anaesthesiol Scand], 2014 Nov; Vol. 58 (10):1165-81
28. Bilgen S; Köner O; Türe H; Menda F; Fiçicioğlu C; Aykaç B. Effect of three different doses of ketamine prior to general anaesthesia on postoperative pain following Caesarean delivery: a prospective randomized study. Minerva Anestesiologica [Minerva Anestesiol], 2012 Apr; Vol. 78 (4), pp. 442-9
29. Vosoughin M; Mohammadi S; Dabbagh A. Intravenous ketamine compared with diclofenac suppository in suppressing acute postoperative pain in women undergoing gynecologic laparoscopy. Journal Of Anesthesia [J Anesth], 2012 Oct; Vol. 26 (5), pp. 732-7
30. Yazigi A; Abou-Zeid H; Srouji T; Madi-Jebara S; Haddad F; Jabbour K. The effect of low-dose intravenous ketamine on continuous intercostal analgesia following thoracotomy. Annals Of Cardiac Anaesthesia [Ann Card Anaesth], 2012 Jan-Mar; Vol. 15 (1):32-8
31. Hu J; Liao Q; Zhang F; Tong J; Ouyang W. Chronic post-thoracotomy pain and perioperative ketamine infusion. Journal Of Pain & Palliative Care Pharmacotherapy [J Pain Palliat Care Pharmacother], 2014 Jun; Vol. 28 (2):117-21
32. Dualé C; Sibaud F; Guastella V; Vallet L; Gimbert YA; Taheri H; Filaire M; Schoeffler P; Dubray C. Perioperative ketamine does not prevent chronic pain after thoracotomy. European Journal Of Pain (London, England) [Eur J Pain], 2009 May; Vol. 13 (5):497-505
33. Ahern TL; Herring AA; Stone MB; Frazee BW. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain.The American Journal Of Emergency Medicine [Am J Emerg Med], 2013 May; Vol. 31 (5):847-51
34. Deng GF; Zheng JP; Wang S; Tian B; Zhang SG. Remifentanil combined with low-dose ketamine for postoperative analgesia of lower limb fracture: a double-blind, controlled study. Chinese Journal Of Traumatology Chinese Medical Association [Chin J Traumatol], 2009 Aug; Vol. 12 (4):223-7
35. Rakhman E; Shmain D; White I; Ekstein MP; Kollender Y; Chazan S; Dadia S; Bickels J; Amar E; Weinbroum AA. Repeated and escalating preoperative subanesthetic doses of ketamine for postoperative pain control in patients undergoing tumor resection: a randomized, placebo-controlled, double-blind trial. Clinical Therapeutics [Clin Ther], 2011 Jul; Vol. 33 (7):863-73
36. Sen H; Sizlan A; Yanarates O; Emirkadi H; Ozkan S; Dagli G; Turan A. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesthesia And Analgesia [Anesth Analg], 2009 Nov; Vol. 109 (5):1645-50
37. Remérand F; Le Tendre C; Baud A; Couvret C; Pourrat X; Favard L; Laffon M; Fusciardi J. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. Anesthesia And Analgesia [Anesth Analg], 2009 Dec; Vol. 109 (6):1963-71
38. Gottschalk A; Durieux ME; Nemergut EC. Intraoperative methadone improves postoperative pain control in patients undergoing complex spine surgery. Anesthesia And Analgesia [Anesth Analg], 2011 Jan; Vol. 112 (1):218-23
39. D. G. Lambert, M. F. Bird and D. J. Rowbotham. Cebranopadol: a first in-class example of a nociceptin/orphanin FQ receptor and opioid receptor agonist. British Journal of Anaesthesia 114 (3):364–6 (2015)
40. V. Martinez, L. Guichard and D. Fletcher. Effect of combining tramadol and morphine in adult surgical patients: a systematic review and meta-analysis of randomized trials. British Journal of Anaesthesia 114 (3): 384–95 (2015)
41. B. M. Mishriky, N. H.Waldron, A. S. Habib. Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis. British Journal of Anaesthesia 114 (1): 10–31 (2015)
42. Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med 2009; 10: 829–39
43. D. Fletcher, V. Martinez. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. British Journal of Anaesthesia 112 (6): 991–1004 (2014)