

Opioid free onco-anesthesia: Is it time to convict opioids? A systematic review of literature

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Abstract

The epidemic of opioid crisis started getting recognised as a public health emergency in view of increasing opioid-related deaths occurring due to undetected respiratory depression. Prescribing opioids at discharge has become an independent risk factor for chronic opioid use, following which, prescription practices have undergone a radical change. A call to action has been voiced recently to end the opioid epidemic although with the pain practitioners still struggling to make opioids readily available. American Society of Anesthesiologist (ASA) has called for reducing patient exposure to opioids in the surgical setting. Opioid sparing strategies have emerged embracing loco-regional techniques and non-opioid based multimodal pain management whereas opioid free anesthesia is the combination of various opioid sparing strategies culminating in complete elimination of opioid usage. The movement away from opioid usage perioperatively is a massive but necessary shift in anesthesia which has rationalised perioperative opioid usage. Ideal way moving forward would be to adapt selective low opioid effective dosing which is both procedure and patient specific while reserving it as rescue analgesia, postoperatively. Many unknowns persist in the domain of immunologic effects of opioids, as complex interplay of factors gets associated during real time surgery towards outcome. At present it would be too premature to conclude upon opioid-induced immunosuppression from the existing evidence. Till evidence is established, there are no recommendations to change current clinical practice. At the same time, consideration for multimodal opioid sparing strategies should be initiated in each patient undergoing surgery.

Keywords: Cancer recurrence, interdisciplinary pain management, onco-anesthesia, opioid free anesthesia, opioid free onco-anesthesia, opioid sparing anesthesia

Introduction

Sir Thomas Sydenham quoted 'Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium'.^[1]

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With the emergence of need of effective pain control, pain was considered an important vital sign for clinical documentation and declared as fifth vital sign.^[2] Pain control started getting equated with quality control in the health system due to administrator governance. The opioid remained the acceptable modality for pain management. The tide of opioid use gradually paved way for prescription misuse and an expected overuse so much so, that in 2017 the United States had to declare an opioid crisis.^[3,4] The need to incorporate opioid

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How to cite this article: Thota RS, Ramkiran S, Garg R, Goswami J, Baxi V, Thomas M. Opioid free onco-anesthesia: Is it time to convict opioids? A systematic review of literature. *J Anaesthesiol Clin Pharmacol* 2019;35:441-52.

Access this article online

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10.4103/joacp.JOACP_128_19

sparing strategies has been emphasised with usage of regional anesthesia techniques as part of multimodal pain management in perioperative setting.^[5] The onus is now on us, to gear up with the change and embrace best practises towards opioid sparing anaesthesia to address the public health care crisis.

At one extreme in the developed world, United States Centre for Disease Control (CDC) issued warning that prescription opioids are the major drug problem.^[3,6] Unfortunately, at the other extreme in the developing world, pain practitioners are still struggling to make opioids readily available to patients undergoing cancer surgeries, highlighting the actual drug problem. This gap is further going to widen if restrictions and impositions are sanctioned against prescribing opioids. To understand the concerns, we conducted this review related to opioid usages and opioid sparing techniques for pain management.

Methodology

The research question for initiating the review was ‘opioid sparing strategies/opioid free anesthesia in Onco-Anesthesia practice’ in which participants, intervention, comparison, outcome and study design (PICOS) format was followed for this review as per the ‘PRISMA’ statement.

The components included were:

Participants

Patients undergoing oncological treatment/surgical procedure.

Intervention

Use of opioid sparing strategies for perioperative analgesia.

Comparison

Opioid free anesthesiapractice.

Outcome

Cancer recurrence, progression, metastatic spread, outcome and overall survival with respect to usage/abstinence from opioids.

Study designs

The review included both prospective and retrospective randomised clinical as well as cohort studies. Relevant editorial review, letter to editor, meta-analysis and review articles were also considered. Isolated case reports, animal studies, *in vitro* experimental studies, studies on human volunteers and case series studies were however excluded.

The explorative search was done from PubMed, PubMed central, Cochrane Library, Google Scholar and Embase

databases for all the related manuscripts from January 2000 till March 2019. The keywords used included opioid use, misuse and abuse, ‘opioid sparing strategies,’ ‘opioid free anesthesia,’ ‘opioid free Onco-anesthesia,’ ‘opioid sparing Oncoanesthesia,’ ‘moving away from opioid based Onco-anesthesia,’ opioid adverse effects including hyperalgesia and tolerance, ‘opioid crisis,’ ‘surgery without opioids,’ ‘opioid and enhanced recovery after surgery,’ ‘regional anesthesia based opioid sparing,’ ‘loco-regional anesthesia in cancer surgery,’ ‘opioid sparing in cancer surgery outcome,’ ‘recurrence, metastasis and survival based cancer surgery outcome with opioid based and opioid sparing/opioid free anesthesia,’ ‘opioids and immune suppression and cancer recurrence,’ non-opioid and non-pharmacologic strategies in acute/chronic pain and opioid alternatives. Further relevant manuscripts were manually searched from the bibliography of the searched manuscripts.

Results

Of the 3000 searched manuscripts, the present review included 116 manuscripts [Figure 1] inclusive of all types of published manuscripts that fulfilled the ‘PICOS’ criteria as defined for our research question. Of these, only 48 manuscripts were reviewed for high quality and non-repetitive content.

The titles, abstract and content were manually screened carefully to assess the suitability for inclusion in the review. The process of screening included factors such as language, available publication data, abstracts with full text availability, its relevance and study type with emphasis on meta-analysis, systematic review, highly relevant review articles, randomised control studies, editorials and retrospective studies in hierarchical order. The characteristics of the studies included are summarised in Table 1.^[2,4,7-51]

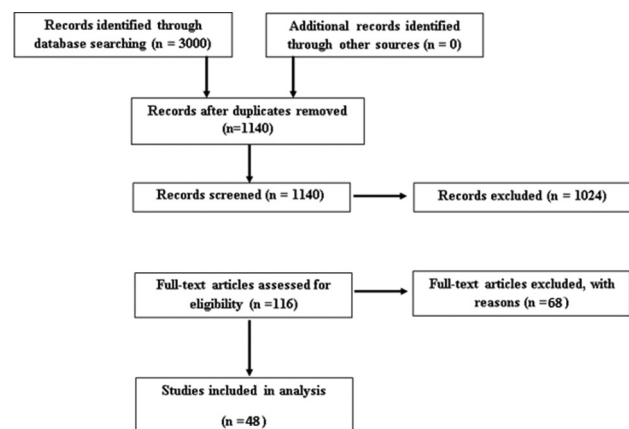


Figure 1: PRISMA flow chart triaging the analysis

Table 1: Individual characteristics of studies included in the review

Principal Author and reference	Type of study	Outcome and objectives	Significance	Inference
Koepke EJ. ^[2] (2018)	Review article	Opioid based sensitisation, tolerance and hyperalgesia propagating to opioid free anesthesia practise.	Opioid paradox in opioid naïve leading to opioid-induced respiratory depression and chronic dependence.	New approach to pain management pyramid putting opioids on top instead of bottom.
Nalini Vadivelu. ^[3] (2018)	Review article	Context of opioid epidemic and opioid crisis.	Origins of opioid crisis described.	Inappropriate prescription of opioids, misuse, abuse and dependence has led to opioid crisis.
Voon P. ^[4] (2017)	Review article	Epidemiology and clinical management of comorbid chronic pain and opioid prescription practises.	Review of relation between chronic non-cancer pain and opioid prescription leading to its abuse.	High-quality evidence is lacking on the prevalence, risk factors and treatment approaches to chronic pain and substance misuse.
Murthy VH. ^[7] (2016)	Editorial	Preventing opioid crisis and opioid-related death (ORD) which have become an important cause of death in the US	Opioid epidemic begins with prescription opioid and in the peri-operative period.	Revolutionise Opioid prescription practices by turn the tide treatment pocket card.
Lavand'homme P. ^[8] (2018)	Review article	Neuro-physiological basis of opioid free anesthesia and patient outcomes.	Opioid sparing and enhanced recovery.	OFA attributes a newer paradigm in anesthesia practise.
Mulier J. ^[9] (2017)	Editorial	Synthetic opioids and its outcome.	Paradigm shift from balanced anesthesia practise to opioid free anesthesia practise.	Survival outcomes in opioid free anesthesia yet to be established.
Fletcher D. ^[10] (2014)	Meta-analysis. A systematic review.	Clinical consequences of opioid-induced hyperalgesia with intra-operative opioid use.	High opioid dosing intra-operatively led to higher postoperative pain.	High dose synthetic opioid remifentanyl had significant increase in acute post-operative pain.
Eckhard Mauermann. ^[11] (2017)	Review	Multimodal opioid free anesthesia in bariatric surgery.	Utility of low opioid dosing in multimodal analgesia.	Low opioid dosing and post-operative use as escape.
Lavand'homme P. ^[12] (2017)	Review chapter	To establish relation between neuroadaptation to opioid use and development of tolerance and opioid-induced hyperalgesia.	Chronic opioid use pre-operatively determines the post-operative opioid consumption which negatively influences surgical outcome.	Direct causal relationship between opioid-induced hyperalgesia and patient outcome is not yet well established.
Forget P. ^[13] (2019)	Review article	Feasibility of OFA	Concept of opioid sparing as against opioid free anesthesia.	Opioid sparing strategies are now recommended
White PF. ^[14] (2017)	Editorial	Balanced anesthesia versus opioid sparing techniques.	Non-opioid and non-pharmacological approaches towards treatment of pain.	Effective pain relief is the need of the hour.
Beloeil H. ^[15] (2018)	Randomised clinical trial. Protocol study	Opioid free anesthesia was hypothesised to reduce opioid consumption and hence opioid-related adverse events.	Allocated patients to receive either an opioid based or an opioid free anesthesia.	The primary outcome to determine opioid-related adverse event in the post-operative period. Results yet to be published.
Sultana A. ^[16] (2017)	Review.	Cancer surgery, sleep apnea, obesity, COPD, complex regional pain syndrome (CRPS) and opioid addiction as indications.	Opioid free anesthesia is a viable concept in bariatric surgery.	Opioid free anesthesia extrapolation possible to cancer surgery- a new avenue to be explored.
Jan P Mulier. ^[17] (2018)	RCT	To evaluate the association between opioid consumption and recovery scores after opioid free anesthesia (OFA) in bariatric surgery.	OFA group had better recovery, lesser pain and favourable cortisol levels.	OFA provides equal hemo-dynamic stability, lesser rescue analgesia, fewer opioid-related adverse events and hasten recovery.
David Samuels. ^[18] (2017)	Retro-spective analysis	Post-operative opioid requirements after opioid-sparing and opioid-free anesthesia.	Comparison of opioid sparing, opioid-based and opioid-free anesthesia groups.	Reduced intra-operative opioid use correlated with reduced post-operative opioid requirements and shorter PACU stay.

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Table 1: Contd...

Principal Author and reference	Type of study	Outcome and objectives	Significance	Inference
Forget P. ^[19] (2017)	Meta-analysis	To establish conclusive evidence on opioid alternatives for attaining hemodynamic stability during surgery.	Both ketamine and magnesium offer hemodynamic stability as well as provide adequate analgesia.	Ketamine and magnesium are excellent opioid alternatives in the context of opioid free anesthesia.
Kamdar NV. ^[20] (2017)	Editorial	Implications of opioid sparing strategies on postoperative outcomes.	Efficient management of post-operative pain as a corner stone of ERAS.	Patient education with OFA & ERAS enhance recovery.
Hontoir S. ^[21] (2016)	Randomised control trial	Assessing postoperative patient comfort in breast surgery.	Quality of recovery assessed in opioid-based and opioid-free groups.	Opioid free anesthesia offers equal comfort and safety.
Daniel B Carr. ^[22] (2017)	Editorial Symposium	Opioid adverse effects and need for multimodal analgesia.	Perioperative opioids from friend to foe. Longer hospitalisation and slower recovery.	Opioid sparing strategies and opioid alternatives.
Sullivan D. ^[23] (2016)	Review article	Opioid sparing multimodal pain management in trauma.	Non-opioid and non-pharmacological treatment strategies described.	Opioid sparing in trauma victims a reality.
Henrik Kehlet. ^[24] (2005)	Editorial	Whether opioid sparing reduces the incidence of opioid-related adverse effects and its effect on recovery as well as morbidity.	Individual opioid sparing of by paracetamol, NSAIDs, COX-2 inhibitor, as well as regional anesthetics, ketamine, gabapentin, pregabalin.	Combined multimodal analgesia achieves highly efficient analgesia along with opioid sparing.
Marret E. ^[25] (2005)	Meta-analysis	Evaluate the risk of opioid adverse effects in patients treated with concurrent non-steroidal anti-inflammatory agents.	22 studies, 2307 patients evaluated. Regression analysis found opioids with higher incidence of nausea and vomiting.	NSAIDs decreased significantly post-operative nausea and vomiting (PONV) and sedation by up to 30%. Other side effects like respiratory depression, retention of urine and pruritus were not affected.
Brandal D. ^[26] (2017)	Prospective Quality Improvement study.	ERAS resulted in embracing opioid free techniques along with multimodal analgesia but did not influence the discharge opioid prescribing practices.	Provides a template towards implementation of protocol based opioid prescription practices at discharge.	Modifying the opioid prescription practices at discharge can influence the outcome of opioid epidemic.
Boland Jason W. ^[27] (2018)	Review article	To compare survival outcomes among patients undergoing regional anesthesia techniques as opposed with systemic opioids.	Non-analgesic immune-modulatory and neuro-endocrine effects of opioids on cellular milieu.	Recommendation towards usage of opioids for cancer pain until definitive evidence against its use emerges.
Connolly Cara. ^[28] (2016)	Review article	Opioid-related outcome after cancer surgery including recurrence and metastasis.	Deleterious to null to potentially protective effects of opioids on cancer outcomes.	Opioids will persist in clinical anesthesia practice until evidence-based recommendations are put forth against.
Meserve JR. ^[29] (2014)	Review article	Quality of life equated with effective cancer pain management.	Regional analgesic techniques may offer survival advantages over opioids.	Clinical studies are not yet convincing.
Garg R. ^[30] (2017)	Editorial	Regional anesthesia and cancer recurrence, immuno-suppression and long-term outcome.	Pain-related immune suppression and need for effective analgesia.	Regional anesthesia provides benefits beyond pain.
Gottschalk A. ^[31] (2010)	Review article	Evaluation of the implication of surgical stress response on the dissemination of cancer cells leading to spread.	The role of peri-operative stress response, neuro-endocrine and inflammatory system in cancer recurrence and spread.	Evidence based conclusion towards cancer recurrence too premature.

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Principal Author and reference	Type of study	Outcome and objectives	Significance	Inference
Sekandarzad. ^[32] (2017)	Review article	Immuno-suppression occurs in a complex peri-operative environment.	Regional anesthesia has not yet been proved to have an added advantage in cancer surgery.	Opioids are safe in cancer surgery as per the new refined animal model studies.
Sekandarzad. ^[33] (2017)	Review article	Complex multi-factorial peri-operative oncological setting defies any conclusion towards RA/opioids in favourable/unfavourable cancer survival outcomes.	Tumour protective effects of RA is controversial and is expected to be so despite ongoing clinical research due to its complexity.	No evidence against opioid-induced cancer recurrence or metastasis from recent refined animal data.
Exadaktylos AK. ^[34] (2006)	Retro-spective analysis	Hypothesis was generated that inclusion of regional technique like paravertebral block with general anesthesia would reduce the incidence of cancer recurrence in breast surgery.	First article to raise questions about cancer outcomes, recurrence and risk of metastasis.	Inclusion of paravertebral block reduced the risk of recurrence and metastasis only during the initial years of follow-up although suggestion was given to evaluate for longer follow-up by further prospective trials.
Cakmakkaya OS. ^[35] (2014)	Review article. Cochrane database.	To establish whether anesthetic technique influence the prognosis and recurrence for patients with malignancy.	General anesthesia compared with regional anesthesia and its combination.	As of now, the evidence towards the benefit of regional anesthesia techniques on the outcome of cancer recurrence is highly inadequate. Prospective randomized controlled trials may add evidence in future.
Oscar Pérez-González. ^[36] (2017)	A systematic review	The effect of regional anesthesia techniques (para vertebral block) on long-term survival outcome in breast cancer surgery.	Recurrence, survival, humoral response and cellular immune response.	Current data neither support nor refute regional anesthesia with recurrence/survival.
Tavare. ^[37] (2012)	Review article	Anesthetics and metastatic recurrence postulated mechanisms.	Anesthetic effects on neuro-endocrine and immune function.	Immune system interactions are complex
Heaney A. ^[38] (2012)	Review article	Relation to surgery, anesthesia factors to immunosuppression and metastasis.	Perioperative factors influencing cancer recurrence and metastasis deciphered.	Anesthesia factors influencing cancer recurrence is inconclusive.
Divatia JV. ^[39] (2014)	Editorial	Regional anesthesia, Volatile agents, opioids and propofol TIVA on cancer recurrence.	Association of anesthetics and immunosuppression is less relevant than tumour biology, pain, transfusion and adjuvant cancer therapies.	Current recommendations would not suggest any drastic practise change in peri-operative cancer treatment.
Das J. ^[40] (2014)	Review article	Anesthetic technique and cancer recurrence are based on foundation of inconclusive evidence.	Blood transfusion, hypothermia, pain, steroids, neo-adjuvant chemotherapy, surgical stress can interfere with immune-modulation.	Immuno-modulation and tumour recurrence cannot be attributed to individual anesthetic agents.
Brack A. ^[41] (2011)	Review article	Opioid-induced immunosuppression and risk of infection.	Coexisting disease can intervene in interpretations of opioid-induced immunosuppression in cancer	Need for selection of refined animal models.
Buggy DJ. ^[42] (2015)	Editorial.	Anesthetic/analgesic technique affecting cancer outcomes not proven	Conflicting data against role of opioids in cancer recurrence or metastasis	Insufficient evidence against change of opioid based clinical practice.
Buggy DJ. ^[43] (2014)	Editorial	Inhalational agents, opioids and high Fio2 put under the scanner	Benefits of regional anesthesia techniques established.	Propofol TIVA, xenon, IV Lidocaine favoured.
Susan M Nimmo. ^[44] (2017)	Review article	Pain management, mobilisation and nutrition fundamental in recovery.	Pain as the major limiting factor in early recovery after surgery.	Effective Pain management important to early recovery.

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Principal Author and reference	Type of study	Outcome and objectives	Significance	Inference
Dario Bugada. ^[45] (2016)	Review article	ERAS as a peri-operative pathway to early recovery.	Multimodal and multi-disciplinary approach with opioid sparing to enhance recovery.	Cancer specific ERAS approach to be developed.
Kim BJ. ^[46] (2016)	Review article	Association between perioperative care and RIOT in perioperative medicine.	Return to intended oncologic therapies (RIOT) is a clinical measure to monitor the functional recovery in cancer surgery after an intervention.	The enhanced recovery techniques utilised in the perioperative period can influence overall cancer survival.
White PF. ^[47] (2018)	Editorial	To evaluate non-pharmacological approaches in pain management.	Opioid abuse continues to pose threat to health care system despite the formulation of CDC guidelines.	Non-pharmacological analgesia offer a value based addition to the multi-modal inter-disciplinary pain management approach.
Kanupriya Kumar. ^[48] (2017)	Review article	Burden of opioids on health care system and opioid sparing strategies.	Opioid sparing effects of non-opioid adjuncts described.	To counter opioid epidemic and develop strategies to mitigate opioid crisis.
Juan P Cata. ^[49] (2016)	Review article	To evaluate whether the expression of opioid receptor and peri-operative opioid usage is associated with cancer progression and its recurrence.	Most of the available clinical studies are retrospective in nature with several confounders. Opioid receptors expression in tumour cells cannot be extrapolated to cancer recurrence and disease progression.	There is no definitive evidence against opioids in the causal of cancer recurrence. Opioids should not be avoided with an isolated goal of reducing cancer recurrence.
Nicholas J. S. Perry. ^[50] (2018)	Review	To validate effects of propofol-based total intravenous anesthesia (TIVA) and volatile anesthesia on survival outcomes.	Inhalational fluranes and TIVA propofol differently influence cancer outcomes.	Although propofol is favoured over inhalational agents in cancer surgery, from an outcome point of view there is no evidence.
Philipp Lirk. ^[51] (2019)	Editorial	Exploring opioid free anesthesia for all surgeries.	Despite opioid crisis, limitations in the availability of alternate analgesics effective to treat severe pain pose realistic threat to practice of OFA.	In the context of multimodal analgesia opioids used in modest dose, for shorter duration remain safe & effective.

Discussion

This systematic review of the literature provided the insight about the appropriate and optimal use of opioids in perioperative setting of the patient undergoing cancer surgeries. Opioid sparing strategies have emerged embracing loco-regional techniques and non-opioid based multimodal pain management, whereas opioid free anesthesia is the combination of various opioid sparing strategies culminating in complete elimination of opioid usage. The recent concerns about the opioid-related misuse and its effects on cancer outcome have been instigated. It justifies the need not to eliminate opioid from practice, but to adapt an effective as well as selectively low opioid dosing which is both procedure and patient specific while reserving it as rescue analgesia postoperatively.

Opioid crisis fact file: The recent concerns related to opioid use/misuse may be attributed to certain facts that need to be understood. Some of these are:

- i. *Opioid use begets opioid use:* The primary treatment of post-surgical pain is opioid. More opioids are prescribed postoperatively for pain control in the pretext of quality of care^[2]
- ii. *'Opioid-paradox':* The more the opioids used intraoperatively, the more shall be the requirement postoperatively. This paradoxical phenomenon is due to sensitisation of opioid receptor and the tolerance developed which further leads to hyperalgesia^[2]
- iii. *Preventing opioid naïve patients from becoming chronic users:* Opioid naïve patients, previously unexposed to opioids undergoing short duration surgery developed opioid dependence by one year after surgery due to faulty iatrogenic prescription practises. Risk factors attributed were young adults with lower income associated with higher intra-operative opioid usage extending beyond the duration of acute post-operative period^[2]
- iv. Repeated morphine doses administered postoperatively prolongs pain further, which may end up in persistent

post-surgical pain (PPSP) in animal models.^[8] Beginning with third post-operative day, each dose of opioid prescription translates to chronic opioid use disorder. About 50% of opioid naïve patients are given an opioid prescription postoperatively, out of whom 3.1% continue to use beyond 3 months contributing to chronic opioid user pool. This has led to an iatrogenic addiction^[2,3]

- v. 75% heroin users admitted having initially started off with a left-over prescription opioid which later led to addiction^[2,3]
- vi. Amidst an increasing trend of opioid-related death, closed claims revealed that 88% of opioid-related death (ORD) occurred within 24 postoperative hours due to undetected respiratory depression especially in the obese. The epidemic of opioid use, misuse and abuse has resulted in significant morbidity as well as mortality.^[3,9] Incidence of opioid-related deaths due to respiratory depression causing hypoxia, brain damage leading to death was 0.1-37%.^[2,10]

Why to switch over from balanced anesthesia to opioid sparing?

Though John Lundy introduced the term 'balanced anesthesia' in 1926, it was Kehlet in 1989 who revolutionised the concept of balanced anesthesia by amalgamating opioids and non-opioids in clinical practise.^[52,53] Prior to the conception of opioids in anesthetic practise in 1960s, high dose thiopental sodium and inhaled anesthetics were being used to achieve hypnosis, amnesia and immobility. Suppression of autonomic response became viable after the introduction of opioids. The inclusion of non-opioids along with opioids synergised the concept of balanced anesthesia by improving postoperative pain control and negating the opioid adverse effects.^[2,13,14,52-54]

The dawn of opioid free anesthesia (OFA)

Opioid free anesthesia (OFA) is defined as the combination of various opioid sparing strategies culminating in complete avoidance of perioperative opioid usage to reduce opioid-induced adverse effects without sacrificing patient comfort.^[13,15,16] OFA ideally includes loco-regional techniques, nonopioid analgesics and antihyperalgesics for an integrated pain management.^[13,55]

Jan Paul Mulier in 2012 proposed OFA in obese patients undergoing bariatric surgery and showed improved outcomes with shorter hospital stay especially in patients with obstructive sleep apnoea.^[16,17,56] Initially a combination of intravenous dexmedetomidine, ketamine and lignocaine were utilised to which newer additions like magnesium sulphate, gabapentin, dexamethasone, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDS), cyclo-oxygenase-2 (COX-2) inhibitors were made subsequently.^[16,56] The addition of local anesthetic infiltration (liposomal bupivacaine) and locoregional

blocks (fascial plane regional blocks, central neuraxial blocks) further enhanced pain management.

The goal of opioid free anesthesia is to rationalise perioperative opioid use by avoiding intraoperative opioids, spare opioids to limited postoperative use at the same time reducing its usage, preventing persistent post-surgical pain, enhancing early recovery without compromising patient comfort.^[8,9,11,13,18,20,55,56] OFA avoids opioid-related adverse effects, tolerance and hyperalgesia that had been taken for granted after general anesthesia.^[9,12] Specific indications for OFA include chronic preoperative pain treated with opioids, opioid substance use disorder, obesity linked obstructive sleep apnoea, complex regional pain syndrome (CRPS) and persistent post-surgical pain (PPSP).

Opioid free anesthesia: A paradigm shift

The movement away from opioid usage perioperatively is a massive but necessary shift in the thinking which has gone beyond the boundaries of bariatric surgery and penetrated onco-anesthesia practise.^[16] This shift has embraced locoregional techniques along with nonopioid based multimodal pain management^[56] [Figure 2] to gear-up the rejuvenation in regional anesthesia practise and rationalising perioperative opioid usage.^[8] It's the shift breaking the link with acute opioid exposure against developing an opioid dependence on chronic exposure which is now being considered with a different regard.^[1,2,8,9,13,55]



Figure 2: Adopted from 'New paradigm in analgesia management'. (With kind permission from Dr. Michael Manning 'The rising tide of opioid use and abuse: Role of Anesthesiologist'. Perioper Med 2018 Jul 3;7:16)

OFA – What about patient comfort?

Hontoir addressed the concerns of patient comfort with opioid free anesthesia and satisfaction scores postoperatively in patients undergoing breast surgery.^[21] The QOR-40 (quality of recovery by 40 questionnaires) scores were utilised for satisfaction scoring.^[21] Both the opioid free and opioid based groups had comparable analgesic requirement postoperatively and at 24 hours.^[21] The only drawback of the study being the utility of piritramide (Meperidine-related weak mu agonist) as the choice of postoperative analgesia hence rendering it not strictly opioid free.^[21]

Are perioperative opioids obsolete? Opioids- being a friend to becoming foe

By including multimodal nonopioid based analgesia, perioperative opioids will no longer be routinely needed as default analgesia if dealt with an integrated multimodal approach.^[10,22] At the same time, no patient should be deprived of opioids if need arises.

Opioid sparing strategies: Looking at opioid alternatives

Multimodal interdisciplinary pain management approach [Figure 3] to opioid sparing has the advantage of using lowest effective opioid dose, lessening the risk of opioid misuse/abuse, combating opioid-induced hyperalgesia postoperatively and allowing safer use of each drug in lower dose with each having a different mechanism of action.^[11,23] There are many benefits of opioid sparing anesthesia strategies [Table 2]. Paracetamol, NSAIDS and COX-2 inhibitors bring about 24–31.6% opioid sparing effect and significant reduction (30%) in opioid-related adverse events.^[24,57] Addition of nonopioid

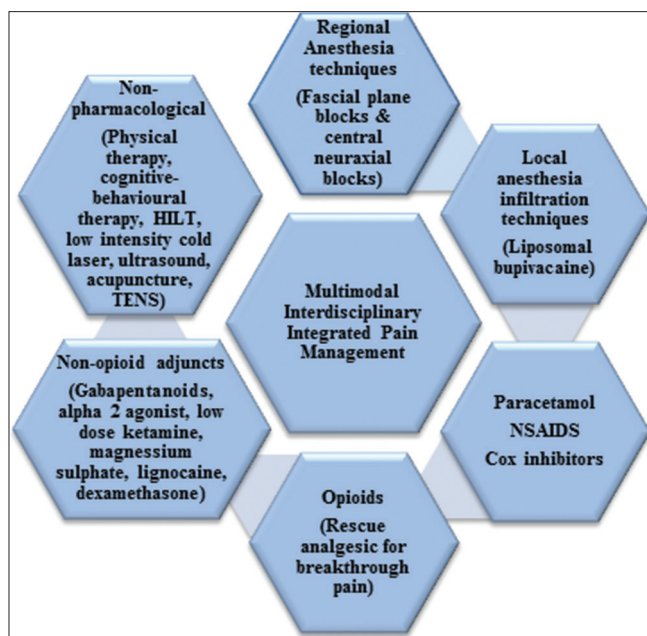


Figure 3: Multimodal Interdisciplinary pain management

adjuncts like α -2 agonist, low dose ketamine, gabapentinoids, magnesium sulphate, dexamethasone adds 20–50% further to opioid sparing.^[23-25,57,58] Non-pharmacological techniques like ultrasound, cold laser, high intensity laser therapy (HILT), cryotherapy, acupuncture, physiotherapy, psychotherapy incorporating cognitive behavioural therapy, electrotherapy involving transcutaneous electrical nerve stimulation (TENS) further alleviate pain postoperatively when used as an integrated interdisciplinary pain management.^[59,61]

Opioid sparing or opioid free anesthesia: Which is the way forward?

The greatest enigma to pain research has been opioid-induced hyperalgesia and persistent post-surgical pain.^[11] Liberal opioid prescription has stemmed the emergence of hyperalgesia (especially continuous remifentanyl infusion with its abrupt withdrawal).^[10] High doses of neuraxial fentanyl have also been linked to higher pain scores and to increase postoperative opioid requirements. Neither of them represents hyperalgesia in the true sense though, as actual central sensitisation is not evident.^[10]

Ideal way moving forward would be to adapt selective low opioid effective dosing, optimising perioperative opioid usage (both procedure and patient specific) and to reserve opioid as rescue analgesia postoperatively.^[3,62,63] Synergistic nonopioid adjuncts, locoregional techniques and non-pharmacologic integral pain therapy will facilitate comfort and enhance recovery.^[26] A critical evaluation of opioid dosing is paramount in each patient. Refraining from use of high dose of perioperative opioids and routine postoperative opioid prescription shall be the responsibility of each pain practitioner in preventing the opioid crisis.

Opioid-induced immunosuppression. Is there evidence?

Many unknowns persist in the domain of immunologic effects of opioids, as complex interplay of factors [Figure 4] influence

Table 2: Benefits of adapting opioid sparing strategies in anesthesia practice

- Modulate neuro-inflammatory-immune mediated stress response.
- Multi-modal and interdisciplinary pain strategies lead to enhanced recovery.
- By keeping Mu receptor virgin-opioid naive remain opioid naive.
- Less prone to overuse, prescription misuse, abuse, addiction.
- Prevent sensitization, tolerance, hyperalgesia.
- Prevent chronic post-surgical pain.
- Early return to intended oncologic treatment.
- Early hospital discharge lead to improved cost control.
- Mitigate opioid related adverse events.
- Prevention of opioid related death.
- Promote regional anesthesia practices and loco-regional anesthesia techniques.
- Mitigate opioid crisis

host immune response.^[27,64-66] To establish causation linked immunosuppression to opioids would be impossible in human studies considering ethical hurdles. In order to reproduce tumour biology and its behaviour with immune system, the clinical outcome studies should be performed on cancer patients undergoing real time surgery assessing the outcome progression prospectively and not by retrospective studies designed for hypothesis generation.^[27,28] Rather, pain itself is immunomodulatory and detrimental along with surgical stress response.^[27,29,30]

At present it would be too premature to conclude upon opioid-induced immunosuppression from the existing evidence.^[29]

Evidence-based recommendations for opioid use in Onco-anesthesia

- i. Are opioids immune modulatory: Immunomodulation effects of opioids in the form of NK cell suppression found in animal studies are not demonstrable in human opioid studies^[27,31,32]
- ii. Are opioids safe to treat perioperative and chronic pain: Clinical studies have failed to demonstrate adverse outcomes in patients receiving opioids for cancer pain.^[28,29] Recent data from refined animal models suggest that opioids are safe^[32]
- iii. Are opioids safe in pediatric pain: No adverse developmental, behavioural and cognitive integral effects of opioids in pediatric population^[10]
- iv. Are opioids implicated in cancer recurrence: Opioid-tumour interaction is complex and not well defined. Opioid effects on cancer recurrence are contradictory and not well established^[27,28,31,67]
- v. Do opioids affect cancer outcomes: Opioid effects on overall cancer survival and outcome are not causal.^[27] There is

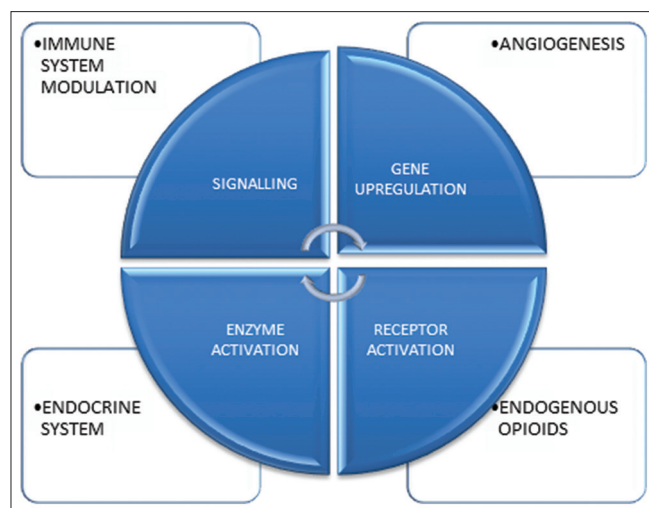


Figure 4: Opioid-tumour interaction with Immune system

no substantial evidence against opioids in the causation of tumour recurrence, spread and metastasis.^[28,33]

Opioid versus regional anesthesia: Evidence?

Studies have linked regional anesthesia with favourable cancer outcomes retrospectively.^[34] The meta-analysis by Cakmakaya *et al.* had suggested no advantage on survival outcome with neuraxial blockade compared with systemic opioids in cancer surgery.^[35] Cochrane review did conclude against any beneficial survival outcomes with regional anesthesia due to lack of quality of evidence.^[32,35]

Regional anesthesia has not been shown to be universally beneficial over opioids (other than superior pain relief and anti-inflammatory effect) with respect to preventing recurrence and influencing outcome in cancer surgery.^[29,31,32,35,36,68,69] Singling out one intervention in a multifaceted, complex, dynamic perioperative setting to establish cancer outcomes would be disastrous.^[28,33] Perioperative opioid sparing leading to better long-term outcome needs to be proven beyond doubt with high quality cancer pain studies until which opioids should continue to be recommended in cancer pain management.^[27,28]

Anesthetic technique and cancer recurrence. Evidence or speculation?

Will anesthetic technique or the choice of analgesic influence cancer outcomes and metastasis? Heaney and Buggy have dissected the association intricately.^[38] Metastatic recurrence remains frustratingly common entity which is invariably difficult to treat.^[37,39] Unfortunately, perioperative period is the most critical window for cancer recurrence considering the multitude factors having an interplay with inflammatory mediators including cytokines, neuromodulators, endocrine system activators, metabolic and immunologic signalling pathways.^[30,31,37] Surgical stress, pain, tumour handling activates numerous biological cascades leading to immunosuppression culminating in perturbations in cellular signalling initiating a cascade of immunoeediting and immunomodulation.^[29,70-72]

Seeding by micro-embolisation allows the spread of cancer which along with the circulating tumour cells (CTC) become responsible for metastasis and recurrence.^[40,70,72] Unfortunately, the surgical procedure intended for cure now creates a period of susceptibility overcoming host defence, leading to dissemination of residual cancer cells into circulation by microembolisation due to tumour handling or by a pre-existent micro-metastasis seeding resulting in an established metastasis.^[37,38,72]

In vitro animal studies and data from retrospective studies with hypothesis generation should not be extrapolated to

evidence.^[41] The choice of opioids, non-opioid adjuncts, regional anesthesia techniques, volatile anesthetics and propofol-based TIVA derived from *in vitro* experimental studies yielding conflicting results (from deleterious to null to protective effects) cannot be considered as evidence towards cancer causation, recurrence, spread and outcome.^[28] Prospective human studies despite ethical hurdles are needed to establish an evidence towards causation of cancer recurrence with the choice of anesthetic technique, which may provide an insight into future.^[41,73]

Till evidence is established, there are no recommendations to change current clinical practise.^[28,42,67] It will be too premature to make any recommendation regarding the ideal anaesthetic technique till results from evidence based prospective human studies become available.^[28,29,41,42] There is no evidence to state that a change in either anesthetic technique or practise could have an impact on survival outcomes in cancer patients.^[28,42,67,74] Opioids shall continue to be a part of multimodal pain management both in the perioperative and in chronic cancer pain management.^[28]

Opioid free anesthesia (OFA) in an era of ERAS

Enhanced recovery after surgery (ERAS) is a multi-dimensional approach to reduce length of hospital stay involving a rational set of perioperative goals targeting early ambulation, gut motility, enhanced nutrition, thromboprophylaxis by integrating goal directed fluid management, ventilatory strategies and optimising perioperative hemodynamics.^[45] The incorporation of aggressive postoperative pain management also targets an early recovery.^[44,45,75]

High dose opioid increases length of hospital stay, delays early recovery and return to normalcy.^[20,26] OFA has favourable profile leading to early recovery (although sedation may hinder early discharge from PACU) and reduction in postoperative hyperalgesia. Enhanced recovery pathway incorporating OFA provides a platform for addressing patients with opioid addiction and ensuring their safe transition into postoperative recovery.^[20]

Goal of ERAS is to provide ‘optimal analgesia’ which optimises patient comfort, facilitates early functional recovery while minimising adverse effects of opioids. Cancer specific ERAS pathway in Onco-anesthesia will be the next big thing happening in cancer research which will be specific to the subtype of cancer surgery.^[45,75,76]

Summary

It is more important to address issues like surgical stress, persistent post-surgical pain, prevention of hyperalgesia,

transfusion-related immunomodulation, hypothermia-related deleterious effects, importance of prewarming, malnutrition correction, improving functional capacity by pre-habilitation and integrating interdisciplinary pain management among cancer patients undergoing surgery rather than to delve upon opioid-induced immune-homeostasis disruption. Opioid sparing strategies involving an emergence of loco-regional techniques is a welcome trend, but not at the expense of opioid conviction. Opioids would still be recommended as the primary rescue analgesia in acute postoperative as well as in the chronic cancer pain management despite the current global opioid epidemic crisis and no patient in need should be deprived of opioids. There is no current evidence to support any change in clinical anesthesia practise. At the same time, consideration for multimodal opioid sparing strategies should be initiated in each patient undergoing surgery. Well, let’s begin opioid sparing...

Acknowledgements

We acknowledge, Michael W. Manning, Assistant Professor, Division of Cardiothoracic Anesthesia, Division of General, Vascular and Transplant Anesthesia, Duke Cardiovascular Research Centre, Duke University, Durham, NC-27710. For permitting the usage of the Figure “New paradigm in analgesia management”, from his article, The rising tide of opioid use and abuse: the role of the anesthesiologist. Perioper Med (Lond).

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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