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Review

Effects of anesthetic and analgesic techniques on cancer metastasis

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ABSTRACT

The rate of mortality and morbidity among cancer patients is at an alarming rate and its ratio of incidence is increasing as a result of its effects of metastasis and recurrence in its patients. Several factors including anesthetic agents and analgesia techniques have been identified as causative agents for cancer metastasis. In this mini-review, we will summarize some of the available effects of anesthetic and analgesic techniques on cancer metastasis as derived from experimental cell culture and live animal data and also form clinical studies.

Contents

1. Introduction

The mortality and morbidityrate of cancer continues to increase and thereby making it a difficult challenge in treating and managing cancer patients [1]. Presently the only available treatment for cancer tumour patients is surgical resection to remove the primary tumour; but it comes without a consequence, metastatic recurrence. Several reports have suggested that several perioperative factors can directly stimulate both cancer cells and cell mediated type of immunity and as such leading to spreading of metastatic tumour [2,3] (Table 1).

The mechanism of metastasis is marked by the separation of cells that shows metastatic properties from the primary tumour and its completion is demonstrated by formation of tumour within a close or usually a distant organ [4,5]. It should be noted that the spreading of a tumour depends majorly on the formation of new blood vessels (angiogenesis) and aggressive attack of the immune system of the host. As described by Fidler, single cell undergoing uncontrollable multiple cycles of cell division and mutation results into a tumour cell [6] that are non-responsive to biological cell signaling that mediates and control normal cell division thereby resulting into uncontrollable tumour growth [7]. Wide-ranging angiogenesis processes are developed in other for a tumour to thrive in terms of growth. However the angiogenesis process is stimulated by the release of, vascular endothelial growth factor (VEGF) and prostaglandin E2 from the evolving tumour [8]. After angiogenesis has been established, metastatic cell separates from the tumour's origin and migrate to neighboring cells [9]. It should be noted that a benign carcinoma tumour transform into a malignant tumour at the onset of the invasion of the basement

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Table 1
Influence of perioperative factors on cancer recurrence and metastasis.

Surgery	Increases neuroendocrine and cytokine stress response Incapacitate cell-mediated immunity [10] Stimulates tumour growth and metastasis in animal models
Volatile anaesthesia	Suppresses the immune activity of leucocytes [11] Connected with induction of apoptosis in lymphocytes in vitro
Opioids	Suppresses cell-mediated and humoral immunity [12] Promote tumour cell migration [13], proliferation, and cancer gene expression in human cells in vitro Facilitate angiogenesis
Propofol	Decreases cancer cell migration, proliferation, and metastasis in vitro Possible COX inhibitor
Pain	NK cell activity was suppressed as reported in animal studies that pain was ineffectively treated postoperative [14].
NSAIDs/COX inhibitors	PGs inhibit NK cell cytotoxicity and modulate the tumour microenvironment Long-term use associated with reduced incidence of cancer [15]
Hypothermia	Stimulates sympathetic nervous system and glucocorticoid release [16] Increases bleeding and allogeneic blood transfusion Suppresses cell-mediated and humoral immunity [17]
Psychological stress	Animal and clinical evidence of an association between stress, depression, and cancer progression Activates HPA-axis and sympathetic nervous system Contributes to perioperative immunosuppression [18]
Allogeneic blood transfusion	Associated with immunosuppression, increased risk of cancer recurrence, and reduced survival

Table 2
Anesthetic Agents.

Drug	Type	Importance
Halothane	Inhalational, halogenated	Upkeep of anesthesia
Isoflurane	Inhalational, halogenated	Upkeep of anesthesia
Sevoflurane	Inhalational, halogenated	Upkeep of anesthesia
Propofol	Intravenous Induction.	Can also be used as continuous infusion for maintenance.
Thiopentone	Intravenous, barbiturate	Initiation of anesthesia.
Lidocaine	Local (short acting)	Infiltration can be used for simple procedures and postoperative pain relief
Bupivicaine	Local (long acting)	Used in regional techniques (spinal, epidural) for intra- and postoperative analgesia and anesthesia
Xenon	Inhalational, noble gas	Upkeep of anesthesia, not widely used clinically due to expense
Nitrous oxide	Inhalational	Adjunct to general anesthesia, reduces need for other inhalational agents; useful analgesic properties

membrane and also invades the systemic circulation of the host cells via the lymphatic systems.

1.1. Local anesthetics and regional anesthesia

Some researchers have reported in their clinical studies of a connected link that exist between the use of regional anesthesia and decreased cancer metastasis [19]. However with these clinical studies, report has also emerged about the use of regional anesthetic techniques leading to lack of the stress response activation in cancer patients. Piegeler and co-worker reported and proposed that the prevalence of cancer recurrence is as such decreased by local anesthetic agents (Table 2) via anti-inflammatory action and a direct effects on the proliferation and migration of cancer cells [20]. In addition Martinsson reported that lidocaine and ropivacaine have been demonstrated to be effective on cancer cells when cultured in-vitro as an s anti-proliferative agent [21]. Sakaguchi also corroborated the effectiveness of lidocaine in his report, that lidocaine was demonstrated to suppress cancer cell proliferation through direct inhibitory action on some specific growth factor receptor responsible for proliferation and differentiation of epithelial cells and tumours of epithelial cell origin [22].

Table 3
Ongoing research investigating the effects of anesthetic agents on immune cell function and metastasis.

Cancer type	Area of investigation	NCT number	Principal investigator
Breast cancer	TIVA vs inhalational anesthesia	2089178	Koo
Breast cancer	Propofol sedation with local infiltration vs general anesthesia with sevoflurane	00938171	Chang
Breast cancer	Regional plus TIVA vs general anesthesia + opioids	418457	Buggy
Breast cancer	TIVA vs inhalational anesthesia	2005770	Beck Schimmer
Pancreatic Cancer	TIVA vs inhalational anesthesia	2335151	Beck Schimmer
Colon/Rectal/Breast cancer	TIVA vs sevoflurane-maintained anesthesia	01975064	Bergkvist
Malignant melanoma	Regional vs general anesthesia	1588847	Van Aken
Colon cancer	Regional vs general anesthesia	684229	Reytman
Colon cancer	Regional vs general anesthesia	2326727	Kurz
Colon cancer	Perioperative analgesia with morphine PCA vs epidural	2314871	Berta
Colon cancer	Epidural anesthesia vs no epidural anesthesia	2326727	Reytman
Tongue Cancer	TIVA vs combined intravenous-inhalational anesthesia vs inhalational anesthesia	1854021	Zhang
Breast cancer	Peritumoral local anesthesia vs no peritumoral local anesthesia	1916317	Badwe

NCT = ClinicalTrials.gov clinical trial number; PCA = patient-controlled analgesia; TIVA = total intravenous anesthesia.