Effect of anesthetic, analgesic and sedative agents on human cell phagocytosis. Review.

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Abstract. Along with preoperative stress, anesthetics *per se* are associated with decreased activity of the immune system. Phagocytosis is an important process where particles, such as dead cells and bacteria, are eliminated from the organism. This process is complex and involves cell chemotaxis, tissue infiltration, several coordinated cellular events and the production of reactive oxygen and nitrogen species (ROS). Therefore, the aim of this review was to report the effects of anesthetic, analgesic and sedative agents on human cell phagocytosis. This review suggests that human phagocytosis processes are affected by main anesthetic, analgesic and sedatives agents that result in decreased chemotaxis, phagocytosis and ROS production. These effects may impair the anti-bacterial function of phagocytes. Clinical anesthesiologists should select the anesthetics and the anesthetic methods with careful consideration of the clinical situation and the immune status of patients, concerning long-term mortality, morbidity, and the optimal prognosis.

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Efecto de los agentes anestésicos, analgésicos y sedativos sobre la fagocitosis celular humana.

Resumen. La anestesia y el estrés preoperatorio están asociados a la depresión del sistema inmunitario. La fagocitosis es un proceso importante destinado a la eliminación de células muerta y microorganismos. Es un proceso complejo que involucra la quimiotaxis celular, la infiltración tisular leucocitaria y la activación de diversos procesos intracelulares coordinados, que incluyen la producción de especies reactivas de oxígeno y nitrógeno (ERON). Por lo tanto, el propósito de esta revisión fue reportar el efecto de agentes anestésicos, analgésicos y sedativos en la fagocitosis humana. Esta revisión sugiere que los procesos relacionados con la fagocitosis humana son afectados por los principales agentes anestésicos, analgésicos y sedativos, que inducen una disminución de la quimiotaxis, fagocitosis y producción de ERON y la función anti-bacterial de los fagocitos. Los anestesiólogos clínicos deben seleccionar los anestésicos y los métodos de anestesia, considerando la situación clínica y el estado inmunitario de los pacientes en relación a la mortalidad, morbilidad y pronóstico óptimo a largo plazo.

INTRODUCTION

Anesthetics are a diverse group of drugs used in the management of pain. The administration of anesthetics is necessary to provide inhibition of individual pain pathways (local anesthesia) or to render a patient unconscious so that surgical procedures can be carried out (general anesthesia) (1). Phagocytosis is a process where cells surround and engulf particles such as dead cells and bacteria. This is important both, for single-cell organisms (to acquire nutrients) and as part of the immune system (to destroy foreign invaders). This process is complex and involves several coordinated events such as membrane remodeling, receptor motion, cytoskeleton reorganization and intracellular signaling (2). Before phagocytosis is accomplished, the phagocyte and the particle must adhere to each other. The mechanisms involved in this attachment depend on the chemical nature of the particle's surface. The capacity of phagocytes to engulf microorganisms plays an important role in the immune defense (3). However, drugs that might impair their engulfing capacity can induce immunosuppression (4). Patients that undergo surgical interventions are exposed to anesthetic and analgesic drugs during the procedure that, together with perioperative stress, may impair phagocytes function and expose to infections (4,5). Therefore, we conducted this review to obtain information regarding the effects of relevant anesthetic, analgesic and sedative agents on human cell phagocytosis. Multiple literature searches were performed from1973 through 2019 using online databases from PubMed, Scielo and Bireme.

EFFECTS OF DRUGS ON HUMAN PHAGOCYTOSIS

Inhaled general anesthetics

Isoflurane

With respect to this inhaled anesthetic agent, studies had shown controversial results. It has been reported to have no effect on phagocytosis (opsonized *E. Coli*) of human neutrophils in patients undergoing elective interventional embolization of cerebral arterio-venous malformations (6). Isofluorane did not alter phagocytosis of latex by human monocytes (7). In vitro exposure to isoflurane for 90 min does not significantly alter the phagocytic capacity (*Escherichia coli*) of neutrophils from women during pregnancy (8). Isoflurane promoted phagocytosis (efferocytosis) of apoptotic cells by macrophages, via upregulation of Mer surface expression, through AMPK-mediated blockade of ADAM17 trafficking to the cell membrane (9). In a gas concentration assay, chemiluminescence, superoxide production, and hydrogen peroxide production induced by opsonized zymosan as a phagocytic stimulus were not altered by isoflurane (10). However, altered phagocytic function due to this drug has been reported. Decreased phagocytosis (opsonized and unopsonized *Listeria monocytogenes*) was reported using this drug in alveolar macrophages from bronchoalveolar lavage obtained during orthopedic surgery (11). Isoflurane exposure also decreased human neutrophil phagocytosis (12).

Halothane

In general halothane induces alteration of phagocytic function of phagocytes. Anesthesia with halothane induced decreased chemotactic, phagocytic and bactericidal activity in patients with pathological injury-effected changes or due to varicose veins of extremities (13). Anesthesia with halothane caused a dose-related depressant effect on human neutrophil phagocytic index and a nitroblue-tetrazolium reduction test in patients undergoing gynecological surgery (14). Anesthesia with halothane induced de-creased release of oxygen-free radicals during the phagocytosis of zymosan A by human neutrophils (15). In an assay gas concentration, chemiluminescence, superoxide production, and hydrogen peroxide production induced by opsonized zymosan as a phagocytic stimulus, were diminished by halothane (10). However, in other studies halothane failed to alter the phagocytic function. In this regard, halothane did not inhibit human neutrophil phagocytosis, degranulation and the enhanced non-mitochondrial respiration associated with phagocytosis function in vitro (16).

Sevoflurane

This drug does not alter neither phagocytosis of human polymorphonuclear leucocytes in bronchoalveolar lavage from patients under anesthesia (17) or phagocytosis (*E Coli*), and oxidative burst of circulating granulocytes and monocytes (18).

Desflurane

This drug does not alter phagocytosis of human polymorphonuclear leucocytes in broncoalveolar lavage from patients under anesthesia (17).

Enflurane

Enflurane causes significantly greater depression of human neutrophil phagocytic index and nitroblue tetrazolium reduction test in patients undergoing gynecological surgery (14) and induces decreased release of oxygen-free radicals during the phagocytosis of zymosan A and *Bordetella pertussis* by human neutrophils (15, 19).

Nitrous oxide

Nitrous oxide decreases neutrophil antibacterial capacity in vitro. Exposure of human whole blood to nitrous oxide decreased the percentage of neutrophils showing phagocytosis, and the amount of ingested bacteria (20). Nitrous oxide also decreases release of oxygen-free radicals during serum-opsonized zymosan and Bordetella pertussis phagocytosis by human neutrophils (19).

Xenon

Phagocytosis (*E Coli*) and oxidative burst of granulocytes were reduced with xe-

non anesthesia, whereas monocytes were not affected (18). However, xenon preserved neutrophil and monocyte antibacterial capacity in vitro. Exposure of human whole blood to xenon increased the percentage of neutrophils showing phagocytosis, and the amount of ingested bacteria. Respiratory burst activity in neutrophils and monocytes was not affected by xenon (20).

Methoxyflurane
No information was found.

Intravenous general anesthetics
Propofol

The intravenous anesthetic agent propofol is used to induce and maintain anesthesia during surgical or other invasive procedures and to sedate critically ill patients (21, 22). Previous studies have shown that this drug has controversial effects regarding the phagocytic functions. This anesthetic drug acts via stimulation of the β_2-subunit of the GABA$_A$ receptors inducing impairment of chemotaxis and phagocytosis (microspheres) of circulating human monocytes and macrophages (23-25). Propofol inhibits phagocytosis (latex beads) via the GABA$_A$ receptor and dysregulation of p130cas phosphorylation in macrophages from patients undergoing general anesthesia (26). In vitro studies have shown that propofol inhibits human neutrophil chemotaxis, phagocytosis and reactive oxygen species (ROS) (O$_2$-, H$_2$O$_2$, OH) production, in a dose-dependent manner (27). In vitro studies have shown that propofol diminishes human neutrophil and monocyte phagocytosis (*E Coli*) and oxidative burst even in clinically concentrations (28). In vitro studies showed that propofol inhibited phagocytosis and killing of *Staphylococcus aureus* as well as *Escherichia Coli* (29). However, other studies showed that propofol failed to alter phagocytosis and associated processes. In this regard, this drug did not alter the phagocytosis of *Staphylococcus aureus* by human monocytes (30) or phagocytosis of *Candida albicans* by human neutrophils (31). Propofol does not alter phagocytosis of human polymorphonuclear leucocytes in broncoalveolar lavage from patients under anesthesia (17) or from patients undergoing coronary artery bypass grafting (32). No alteration of human neutrophil phagocytosis (opsonized *E. Coli*) using propofol, in patients undergoing elective interventional embolization of cerebral arterio-venous malformations, has been reported (6). No alteration on phagocytosis (opsonized and unopsonized *Listeria monocytogenes*) was reported using this drug in alveolar macrophages from bronchoalveolar lavage obtained during orthopedic surgery (11). Propofol at the higher concentration failed to reduce both respiratory burst and phagocytosis (*Staphylococcus aureus*) of human neutrophils (33). Propofol exhibited no significant effects on human neutrophil oxidative burst and phagocytosis (*E. Coli*) in patients with severe brain injury requiring long-term sedation (34). Propofol, at clinically relevant concentrations, reduces chemotaxis but fail to reduce phagocytosis of human neutrophils (35). In addition, propofol stimulated human microglial phagocytosis in vitro (36).

Ketamine

Controversial results regarding the effect of ketamine have been reported. Clinically relevant concentrations of ketamine can suppress macrophage function of phagocytosis, its oxidative ability, and inflammatory cytokine production, possibly via reduction of the mitochondrial membrane potential (37). Ketamine significantly inhibited both phagocytosis (*Staphylococcus aureus and Escherichia coli*) and bactericidal activity by human neutrophils (38). In vitro studies have shown that ketamine diminishes human monocyte phagocytosis (*E Coli*) at high concentrations (28). However, other studies showed no effect on the phagocytic function of phagocytes. In his regard, ketamine did not adversely affect phagocytic function of human neutrophils at relevant therapeutic concentrations (39). No depressed phagocytosis and ROS production of human neu-

trophil was observed in vitro by the use of ketamine at clinically concentrations (40). Ketamine at a higher concentration fail to reduce both respiratory burst and phagocytosis (*Staphylococcus aureus*) of human neutrophils (33).

Etomidate

In vitro studies have shown that this drug significantly inhibited both phagocytosis (*Staphylococcus aureus and Escherichia coli*) and bactericidal activity (41).

Thiopental

Thiopental at clinically relevant concentrations reduced both chemotaxis and phagocytosis of human neutrophils (35) and at the higher concentration reduced both respiratory burst and phagocytosis (*Staphylococcus aureus*) of human neutrophils (33). In vitro studies showed that thiopental decreased human neutrophil chemiluminescence (respiratory burst) and phagocytosis (*Staphylococcus aureus and Escherichia coli*) at clinical drug concentrations in a dose-dependent fashion (42). According to this, Nishima et al (40) reported that thiopental was capable of decreasing at clinically relevant concentrations chemotaxis, phagocytosis, and reactive oxygen species (ROS) (O_2-, H_2O_2, OH) production of human neutrophils. The impairment of phagocytic function (microspheres) has also been reported in human monocytes, mediated via stimulation of $GABA_A$ receptors by thiopental (25). In addition, thiopental can also depress the phagocytosis of *Staphylococcus aureus* by human monocytes (43). In vitro studies have shown that thiopental diminishes human neutrophil and monocyte oxidative burst induced after phagocytosis (Staphylococcus aureus and Escherichia coli) at high concentrations (28, 38).

Sedatives and tranquilizers

Dexmedetomidine

Dexmedetomidine is a highly-selective α_2-adrenergic receptor agonist used for sedation of critically ill patients in an intensive care setting and as adjuncts to anesthesia.

Previous studies have shown that clinical doses of this drug has no effects on chemotaxis, phagocytosis or superoxide anion (O_2-) production of human neutrophils, suggesting that this drug may be useful in patients with infection, sepsis, or systemic inflammation (5). According to this, *in vitro* studies have shown that clinically relevant concentrations of dexmedetomidine do not affect chemotaxis, phagocytosis, or superoxide production by human neutrophils (44). However, decreased human neutrophil phagocytosis of *E. Coli,* associated with suppressed respiratory burst, nitric oxide (NO) production, and induced nitric oxide synthase (iNOS) activity induced by dexmedetomidine have been reported (45).

Clonidine

This is a α_2-adrenergic receptor agonist also used as adjuncts to anesthesia. Chemotaxis, phagocytosis and further production of superoxide anion of human neutrophils, are not altered by the used of this drug (5) and *in vitro* studies had shown that clinically relevant concentrations of clonidine do not affect chemotaxis, phagocytosis, or superoxide production by human neutrophils (44). However, this drug inhibits phagocytosis of cultured human trabecular meshwork cells (isolated from the juxtacanalicular and corneoscleral regions of the human eye) (46).

Xylazine

This alpha2-agonist had no effects on chemotaxis, phagocytosis, or superoxide anion (O_2-) production of human neutrophils; the lack of effect of this drug has also been reported by *in vitro* studies (5, 44).

Barbiturates

Methohexital

It has been reported that this barbiturate is capable of decreasing the phagocytosis of viable *S. aureus* by human monocytes (43). In vitro studies showed that methohexital inhibited granulocyte recruitment and phagocytosis activity (*S. aureus*) in a dose-dependent manner (47). However, other studies show that it failed to alter

the phagocitic function. In this regard, this drug did not influence human neutrophil chemiluminescence (respiratory burst) in a dose-dependent fashion (42). Methohexital exhibited no significant effects on human neutrophil oxidative burst and phagocytosis (*E. Coli*) in patients with severe brain injury requiring long-term sedation (34).

Pentobarbital

This drug did not influence human neutrophil chemiluminescence (respiratory burst) in a dose-dependent fashion (42).

Phenobarbital

In vitro studies showed that phenobarbital decreased human neutrophil chemiluminescence (respiratory burst) in a dose-dependent fashion (42).

Thiamylal

Subclinical doses of thiamylal caused enhancement of the human phagocytic activity of neutrophils, however, super-clinical doses of thiamylal inhibited phagocytic activity of these cells (39).

Amobarbital

No information was found.

Benzodiazepines

Diazepam

This benzodiazepine did not alter phagocytic function (microspheres) in human monocytes (25). In addition this drug in concentration-dependently doses increased chemotaxis and phagocytosis in isolated human neutrophils by Ca2+ -independent mechanisms (48). However, diazepam is inhibitory *in vitro* for the phagocytic functions being its action mediated via specific receptors on immunocompetent cells (49).

Midazolam

At clinically concentrations this intravenous anesthetic depress human neutrophil phagocytosis and further production of ROS (40). In vitro studies have shown that midazolam diminishes human neutrophil oxidative burst after phagocytosis (*E Coli*) at high concentrations (28), but failed to reduce both respiratory burst and phagocytosis of *S. aureus* (33).

Flunitrazepam

In vitro studies showed that this drug significantly inhibited both phagocytosis (*Staphylococcus aureus and Escherichia coli*) and bactericidal activity (41).

Alprazolam

Alprazolam increases human neutrophil phagocytosis of bacteria and further killing and monocyte phagocytosis without modifying antibacterial activity values (50).

Lorazepam

No information was found

Phenothiazines

Promethazine

In general this drug alters the production of ROS, necessary to destroy ingested bacteria. Promethazine predominantly affected the ability of macrophages to produce O_2- during phagocytosis (51). Promethazine also affected the ability of human neutrophils to produce O_2- and hexose monophosphate shunt activity during phagocytosis (opsonized zymosan) (52, 53).

Chlorpromazine

Chlorpromazine increases killing activity against *S. aureus* phagocytosed by human monocyte-derived macrophages (54).

Acepromazine

No information was found.

Opioids

Fentanyl

Fentanyl failed to inhibit receptor expression, phagocytosis and reactive oxygen production by monocytes in clinically relevant as well as supraclinical concentrations (55). Intravenous injection of fentanyl did not alter human neutrophil phagocytic function and superoxide anion generation (56, 57). In addition, *in vitro* studies showed that fentanyl did not influence phagocytosis as well as bactericidal activity in human neutrophils (41). However, high-dose fentanyl anesthesia in patients undergoing coronary bypass surgery showed decreased phagocytosis of zymosan, *S. aureus* and *E. coli* by human granulocytes (58).

Alfentanil

In vitro studies showed that alfentanyl did not influence phagocytosis as well as bactericidal activity in human neutrophils (41). However, this drug alters phagocytosis of latex by human monocytes (7).

Remifentanil

No information was found.

Sufentanil

No information was found.

Butyrophenones

Droperidol

This drug is used as a sedation adjunct to general anesthesia. In vitro studies showed that droperidol caused a significant inhibition of phagocytosis as well as bactericidal activity in human neutrophils (41).

Local Anesthetics

Bupivacaine

In vitro studies showed that bupivacaine alters phagocytic functions. In this regard, this drug inhibited priming of LPS on human neutrophils (59). Bupivacaine in a time-dependent manner diminished phagocytosis, bacterial uptake, oxidative burst and CD11b expression by human neutrophils (43). Bupivacaine impairs surface receptor expression Fc gamma receptor III (CD16), complement receptor 1 (CD35) and complement receptor 3 (CD11b) and may thereby contribute to reduced phagocytic activity and oxidative burst (60). Other studies report different effect of this drug. In vitro studies showed that bupivacaine did not alter the chemotaxis, phagocytosis and oxidative burst of human neutrophils at clinically doses (61, 62).

Lidocaine

Lidocaine inhibited adhesion, chemotaxis, phagocytosis, and the production of superoxide anion and hydrogen peroxide by neutrophils and macrophages (62, 63). Lidocaine also diminished phagocytosis, bacterial uptake, oxidative burst and CD11b expression in human neutrophils, in a time-dependent manner (30, 61). In vitro studies showed that lidocaine inhibited priming of LPS on human neutrophils (59).

Procaine

Procaine inhibits adhesion, chemotaxis, phagocytosis, and the production of superoxide anion and hydrogen peroxide by neutrophils and macrophages (63). Procaine also inhibited the phagocytosis of latex particles by normal monocytes (64). In vitro studies showed that procaine inhibited priming of LPS on human neutrophils (59).

Tetracaine

In vitro studies showed that tetracaine inhibited priming of LPS on human neutrophils (59), and inhibited adhesion, chemotaxis, phagocytosis, and the production of superoxide anion and hydrogen peroxide by neutrophils and macrophages (63).

Mepivacaine

Mepivacaine inhibits adhesion, chemotaxis, phagocytosis, and the production of superoxide anion and hydrogen peroxide by neutrophils and macrophages (63).

CONCLUSIONS

The accumulated evidence described above suggests that human phagocytosis processes seem to be more sensitive to the main anesthetic, analgesic and sedatives agents, which results in decreased chemotaxis, phagocytosis and ROS production and leads to impairment of the anti-bacterial function by phagocytes (Table I). However, different results between those obtained from patients and those obtained from *in vitro* experiments, have been reported. Probably direct information obtained from patients before and after surgery, represents a closer view of real effect of anesthetic drugs. In addition, the attenuation of the preoperative stress responses, by a combination of sedative drugs with general anesthesia, can protect surgical patients from further alteration of phagocytosis processes during the preoperative period. This is very important in patients with risk of microorganism infec-

tions. Other situation to be analyzed is the combination of different drugs used during anesthesia and the final effect of that combination and the preparation of drugs used for anesthesia (65). The negative consequences associated with preoperative immunosuppression, such as an increased risk of postoperative infection, could be decreased by the optimal selection of anesthetics and anesthetic techniques. Concerning the stress response induced by anesthesia, intravenous anesthesia may be superior to inhalation anesthesia in reducing hypothalamic-pituitary adrenal axis activation (66). In the future, anesthetic protocols may be chosen not only for their anesthetic and analgesic effects, but also for their immunomodulatory effects, considering the underlying conditions for which the patients need to be anesthetized (4, 67-69).

Neuraxial anesthesia provide several advantages over other anesthetic agents, including decreased risk of infection through attenuation of the stress response and preservation of immune function (70-73). Despite these benefits, patients with altered immune status are often not considered candidates for neuraxial techniques because of the risk of infection (74).

Despite these documented effects on human phagocytosis, the clinical importance of anesthesia-mediated changes in perioperative immunosupression remains uncertain. Currently, there are no clinical studies evaluating the influence of choice of anesthesia and analgesia on the outcome after oncologic surgery or in immunocompromised patients.

In general, the drugs used during anesthesia induce suppressed phagocytosis processes; therefore, the anesthetic protocols may be chosen not only for their anesthetic and analgesic effects, but also for their immunomodulatory effects. There is evidence suggesting that the choice of anesthetic is important when considering the underlying condition of the particular patient.

TABLE I
EFFECT OF ANESTHETIC, ANALGESIC AND SEDATIVE AGENTS ON HUMAN PHAGOCYTOSIS PROCESSES

Agents	Effect on phagocytosis processes	References
Isoflurane	↓/ne	Lieners et al., 1989 (10); Carrera et al., 1993 (7); Clark et al., 1993 (8); Kotani et al., 1998 (11); Heine et al., 2000 (6); Du et al., 2017 (9); Koutsogiannaki et al., 2019 (12)
Halothane	↓/ne	Nunn et al., 1979 (16); Barth et al., 1987 (15); Lieners et al., 1989 (10); Khan et al., 1995 (14); Ciepichał and Kübler, 1998 (13)
Sevoflurane	ne	Erol et al., 2009 (17); Fahlenkamp et al., 2014 (18)
Desflurane	ne	Erol et al., 2009 (17)
Enflurane	↓	Perttilä et al., 1986 (19); Barth et al., 1987 (15); Khan et al., 1995 (14)
Nitrous oxide	↓	Perttilä et al., 1986 (19); De Rossi et al., 2002 (20)
Xenon	↓/ne	De Rossi et al., 2002 (20); Fahlenkamp et al., 2014 (18)
Propofol	↓/ne	Ince et al., 1988 (24); Krumholz et al., 1994 (29); Skoutelis et al., 1994 (35); Davinson et al., 1995 (33); Mikawa et al., 1998 (27); Heller et al., 1998 (28); Kotani et al., 1998 (11); Heine et al., 2000 (6); Bali and Akabas, 2004 (23); Corcoran et al., 2006 (32); Huettemann et al., 2006 (34); Ploppa et al., 2008 (30); Shiratsuchi et al., 2009 (26); Erol et al., 2009 (17); Wheeler et al., 2011 (25); Yu et al. 2011 (36); Bravo et al., 2019 (31)

TABLE I. *CONTINUACIÓN*

Agents	Effect on phagocytosis processes	References
Ketamine	↓/ne	Krumholz et al., 1995 (38, 41); Toyota et al., 1995 (39); Davinson et al., 1995 (33); Heller et al., 1998 (28); Nishina et al., 1998 (40); Chang et al., 2005 (37)
Etomidate	↓	Krumholz et al. 1995 (38, 41)
Thiopental	↓	Salo and Perttilä et al., 1989 (19); Skoutelis et al., 1994 (35); Weiss et al., 1994 (42); Davinson et al., 1995 (33); Krumholz et al. 1995 (38, 41); Heller et al., 1998 (28); Nishina et al., 1998 (40); Ploppa et al., 2008 (43); Wheeler et al., 2011 (25)
Dexmedetomidine	↓/ne	Nishima et al., 1999 (44); Anderson et al., 2014 (5); Chen et al., 2016 (45)
Clonidine	↓/ne	Wang et al., 1994 (46); Nishima et al., 1999 (44); Anderson et al., 2014 (5)
Xylazine	ne	Nishima et al., 1999 (44); Anderson et al., 2014 (5)
Methohexital	↓/ne	Weiss et al., 1994 (42); Huettemann et al., 2006 (34); Ploppa et al., 2006 (47); Ploppa et al., 2008 (30, 43)
Pentobarbital	ne	Weiss et al., 1994 (42)
Phenobarbital	↓	Weiss et al., 1994 (42)
Thiamylal	↓	Toyota et al., 1995 (39)
Diazepam	↓/ne	Covelli et al., 1991 (49); Marino et al., 2001 (48); Wheeler et al., 2011 (25)
Midazolam	↓/ne	Davinson et al., 1995 (33); Heller et al., 1998 (28); Nishina et al., 1998 (40)
Flunitrazepam	↓	Krumholz et al., 1995 (41)
Alprazolam	↑	Covelli et al., 1993 (49)
Promethazine	↓	DeChatelet et al., 1973 (53); Trush and Van Dyke, 1978 (52); Traykov et al.,1997 (51)
Chlorpromazine	↑	Ordway et al. 2002 (54)
Fentanyl	↓/ne	Perttilä et al., 1986 (58); Krumholz et al., 1995 (41); Welters et al., 2000 (57); Yeager et al., 2002 (56); Menzebach et al., 2004 (55)
Alfentanil	↓/ne	Carrera et al., 1993 (7); Krumholz et al., 1995 (38)
Droperidol	↓	Krumholz et al., 1995 (38)
Bupivacaine	↓/ne	Welters et al., 2001 (60); Mikawa et al., 2003 (61); Jinnouchi et al, 2005 (59); Ploppa et al., 2008 (30); Kawasaki et al., 2010 (62)
Lidocaine	↓	Mikawa et al., 2003 (61); Azuma and Ohura, 2004 (63); Jinnouchi et al, 2005 (59); Ploppa et al., 2008 (30); Kawasaki et al., 2010 (62)
Procaine	↓	Jurjus et al., 1988 (64); Azuma and Ohura, 2004 (63); Jinnouchi et al, 2005 (59)
Tetracaine	↓	Azuma and Ohura, 2004 (63); Jinnouchi et al., 2005 (59)
Mepivacaine	↓	Azuma and Ohura, 2004 (63)

ne: no effect.

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