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Review Article

Appropriate Therapeutic Interventions for ICU Disorders Relating to Pain Relief, Sedations, and Psychological Disturbances

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Abstract

Surgical ICU patients often experience myriad ICU-related symptoms that accompany their primary diagnosis. Pain, anxiety, sleep disturbance, sleep deprivation, agitation, confusion, delirium, complications associated with polypharmacy are just a few examples. Pharmacological therapy prescribed by intensivists to manage some of these symptoms is itself not without side effects. This makes symptom control and relief in the ICU a very complex problem that needs to be individualized for each patient using a multi-modal approach. In this paper we will present an overview of some of the problematic areas in the evaluation and management of the critically sick ICU patients, and will address some of the pertinent, and sometimes easily overlooked, problems associated with the different ICU treatment modalities that are commonly applied.

Keywords: *Delirium; Sleep Deprivation; Pain; Depression; Narcotics*

Symptoms such as extreme pain, fear, sleep deprivation, agitation and severe anxiety are common in intensive care unit (ICU) setting and are often overlooked. Holland et al. [1] have shown that sedatives and pain medications can sometimes be prescribed to satisfy the expectations of the medical providers, or to provide a convenient nursing protocol, rather than providing an effective response to the actual needs and fears of the patient [2]. Effective symptom relief is often associated with amelioration of the patient's complaints even if the underlying disease is not completely controlled. Historically, even before the advancement of Western medicine, pain and discomfort have concerned every patient and physician alike, and every attempt was taken to alleviate them, at times without much success. Despite major advances in technology, pharmacology, and pain management techniques, pain in the ICU patient remains a complex problem that may be under-evaluated or poorly controlled.

Discomfort, pain, fear, anxiety, agitation, and sleep deprivation result in physiologic and psychological stress with important sequelae [3,4]. Stress-related catecholamine surges result in hemodynamic disturbances and manifest as hypertension, tachycardia, and cardiac ischemia and arrhythmias. The neuroendocrine stress response increases production of adrenocortical hormones (corticotropin, cortisol, and aldosterone), angiotensin, antidiuretic hormone, and catecholamines, resulting in hyperglycemia, protein catabolism, fluid retention, and electrolyte disturbances. The negative protein balance can lead to poor wound healing and a depressed immune response. The circadian rhythm is reversed, leading to further neuroendocrine and sleep disturbances [5-7]. Psychological consequences of pain include insomnia, depression, anxiety, and psychosis [8-10]. It is not surprising that the posttraumatic stress disorder (PTSD) is increasingly reported among patients in the ICU, particularly those who experience respiratory disorders requiring ventilator support. Moreover, patients who are placed on high doses of barbiturates, narcotics and benzodiazepines often subsequently develop dependence and acute withdrawal states.

The ICU environment

Evaluating pain and anxiety

The inability to evaluate pain, mental distress, suffering and other psychological issues is a major problem in the management of ICU patients. Critically ill patients are often too ill to verbalize their feelings or accurately express their perception of pain at all times. Patients on ventilators have a minimal ability to communicate, especially if muscle relaxants are used to facilitate neuromuscular blockade. Their sensorium is frequently altered by delirium and confusion, making evaluation even more difficult. Psychosomatic symptoms may be the only manifestation of pain in ICU patients, manifesting as agitation or combativeness. Examples include patients pulling on intravenous catheters, endotracheal or nasogastric tubes, surgical drains, urinary catheters, chest tubes, or fighting the ventilator. Although widely practiced, the use of restraints and muscle relaxants to control these symptoms is not a good alternative to proper pain management. One study reported inadequate pain control in more than 70% of medical intensive care patients [11], with the administration of adequate doses of pain medication in less than half of these patients. Physicians often underestimate effective dose ranges for analgesics, overestimate their duration of action, and fear the dangers of addiction even if doses are within therapeutic ranges. Other investigators have found both inadequate amounts of analgesics prescribed and inadequate dosing intervals for those small amounts that were prescribed [12,13]. Two additional recent studies have found that ICU nursing providers often failed to assess and manage pain appropriately, even when clear indications and appropriate doses of analgesics were ordered [14,15]. Many physicians are not adequately trained in area of pain management or lack the ability to comprehensively evaluate physical as well as psychological pain and suffering.

Intensive care unit protocols

Many ICUs rely on protocols for pain relief and sedation. These protocols are often not tailored to the specific needs of each patient. Extremely ill patients may not tolerate the medications and doses commonly used because of labile hemodynamic profiles, yet they continue to experience intense pain. Narcotics, although widely used, may not be the best analgesic option in all circumstances because of the associated hypotension and respiratory depression. Similarly, hypovolemic and hypotensive patients may not tolerate the sympatholytic effects of epidural local anesthetic protocols.

Priority of care

Pain relief is typically not the highest priority for ICU providers, and is often overlooked because other areas of medical care are perceived to be of greater importance. Hemodynamic monitoring and support, manipulation of respiratory parameters on sophisticated respirators, and other monitoring modalities of physiologic functions often take precedence over comprehensive evaluations of the patient's pain and the patient's feelings. In the present era of electronic charting, the current model requires the intensive care nursing to spend more and more time at the computer terminal for charting and data entry or coordinating the care with other providers, such as respiratory therapists, pharmacists and other consulting teams.

Attitudes

Pain management in most ICUs reflects the attitude as well as the aptitude of the clinicians and nursing staff. Effective pain management may not be achieved if the clinician feels comfortable with only one pharmacological regimen. In the United States, intensivists may be internists, like cardiologists, pulmonologists or nephrologists, or they may be surgeons. Expertise in pain management or airway management may therefore vary widely among providers. ICU pain management protocols are standardized to all patients regardless of the individual patient's needs. Additionally, hospital pharmacy policies may have additional restraints on pharmaceutical agents or quantities allowed to be prescribed and dispensed. Some of these policies intended to safeguard appropriate access to these medications may at times result in delayed, inadequate or inappropriate therapy and pain relief. Despite the widespread increase in the variety and

availability of analgesic medications and regional techniques, the control of pain is often not achieved in the ICU patients, because of their rapidly changing clinical state. An intensivist who is well-versed in pain management and who is willing to evaluate the patient's pain and sedation requirements on a minute-to-minute basis is required. The implications of interventions used in the ICU on pain management and vice versa can only be fully appreciated by an intensivist-pain management expert.

Psychological implications

Patients in the ICU often suffer from psychological and emotional disturbances as a result of pre-existing conditions, disease states, pharmacological interventions, or imbalance of the neuroendocrine system. Posttraumatic stress syndrome is increasingly recognized in ICU patients. Anxiety, depression, and psychosis are common in ICU patients, yet they remain under-diagnosed leading to major psychological impact on the patients and their families [8-10]. We have often seen patients with advanced directives stating that they desire no ICU admissions or ventilator support, because of negative past ICU experiences they or their family members have had.

Pain relief in the ICU

Intravenous analgesics

Analgesic requirements vary greatly within and between different types of ICU patients. Postoperative, cancer, and trauma patients generally require more aggressive pain relief compared to other ICU patients. The ongoing stress, the possible underlying opioid tolerance or addiction can significantly modify the pain threshold of patients. Opiates are the most frequently used medications for pain relief. Naturally occurring opiates (namely, hydromorphone, morphine) are still more popular than synthetic narcotic drugs such as fentanyl. Morphine may be administered by intermittent intravenous boluses, continuous intravenous infusion, or epidural infusion. Patient-controlled analgesia is useful in appropriate patients with a clear sensorium. Morphine requirements vary greatly, since its pharmacokinetics can be significantly altered by renal, cardiac, and hepatic impairments. Morphine's major side effect is respiratory depression in the spontaneously breathing patients. It can delay weaning and liberation from ventilators in intubated patients. Hypotension and increased fluid requirements can occur secondary to venodilatation and histamine release. Paralytic ileus is also a common problem. Narcotic bowel syndrome contributes to increases in patients' mortality, morbidity and can prolong the ICU stay. Pupillary reflexes are affected and can confuse evaluation of neuro-surgical patients. Morphine also can cause biliary spasm. Short-acting synthetic narcotics such as fentanyl, alfentanil, and remifentanil can be used as alternatives to morphine. They offer potent analgesia with a short duration of action and are therefore ideal for use as continuous infusions. Marked respiratory depressant effects, however, can limit their use in patients who are not intubated. They are therefore most suitable for patients on ventilators. Bradycardia also may be troublesome in some patients. Remifentanil is increasingly being used in the ICU because of its very short duration of action, but its cost has limited its widespread use.

Epidural and other regional techniques

Regional techniques are most popular in the acute postoperative and trauma settings. The most commonly used local anesthetics are lidocaine, ropivacaine and bupivacaine. Ropivacaine is increasingly used because of reduced cardiac toxicity compared with bupivacaine. Lumbar epidural analgesia is typically used for patients who have had lower abdominal surgery. Thoracic epidural infusions are useful in patients who have chest and upper abdominal incisions and those with rib fractures. Intrapleural or intercostal catheters and other regional blocks can also provide effective analgesia in many of these patients. An epidural infusion using a combination of local anesthetic together with an opiate such as morphine, hydromorphone, fentanyl, or sufentanil can provide a more effective pain relief while using a more dilute concentration of each agent. Delayed respiratory depression and CO_2 retention are more common with water-soluble opiates, such as morphine, and are due to diffusion from the epidural space into cerebrospinal fluid and cephalad spread to the respiratory center in the brain stem. Acute respiratory depression may be observed with all epidural opiated due to systemic absorption. Other side effects of epidural techniques include nausea, vomiting, pruritus, and urinary retention.

Neuroaxial blocks are contraindicated in patients with coagulation disorders, spine pathology and sepsis. Coagulation disorders are common in the ICU and may be due to thrombocytopenia, disseminated intravascular coagulation, massive blood transfusion, or sepsis. Thus, the role of regional techniques in postoperative patients with these disorders is limited.

Ketamine and ketamine mixtures

Ketamine has amnesic, sedative, and analgesic properties. It is also a bronchodilator and mild respiratory stimulant. Psychotomimetic manifestations constitute its major side effects, and can be effectively ameliorated by the addition of midazolam and possibly opioids. Opioids, such as fentanyl, in small doses, potentiate ketamine's analgesic effects. Continuous intravenous analgesic mixtures containing ketamine are especially useful for patients with moderate to severe pain who have contraindications to regional anesthesia. Ketamine may be combined with midazolam and/or fentanyl in order to cut down on the total doses administered. It also helps in minimizing the hyperalgesia associated with the use of opioid therapy. The addition of midazolam is useful in patients with significant anxiety and opioid tolerance. It also provides amnesia for patients receiving mechanical ventilation. In septic patients, ketamine has been shown to lower kinins and tumor necrosis factor levels. It may also have brain-protective properties via blockade of the N-methyl D-aspartate (NMDA) receptors, and may therefore be useful in patients who have suffered a cardiac arrest or who are at risk of developing hypotension and hypoxemia.

Sedation in the ICU

Sedation may be required in medical or surgical patients who suffer from significant anxiety, restlessness, and confusion. Patients in the ICU exhibiting psychomotor agitation frequently pull at endotracheal tubes, chest tubes, drains, and intravascular catheters and other monitors. Careful sedation helps control these symptoms. Patient discomfort and complaints may appear trivial to ICU personnel, but often are very worrisome to patients. Small doses of opioids may be used as sedatives, especially for patients on ventilators. Sedatives are mandated for all patients receiving neuromuscular blocking agents in order to provide adequate amnesia.

Benzodiazepines have become very popular sedatives in the ICU two decades ago. Diazepam and lorazepam are long-acting medications that may be difficult to titrate, but are still very useful in the management of withdrawal states associated with seizures. Midazolam is a short- acting benzodiazepine that has increasingly replaced these two agents. It is water soluble and can be easily titrated in small intravenous boluses or as a continuous infusion. Respiratory or circulatory depression is generally minimal, and even after prolonged infusions its effects usually dissipate within 2 hours after the infusion is stopped. An infusion of a combination of midazolam with fentanyl and ketamine is very useful in ICU patients experiencing significant pain, or those requiring invasive ventilator support, or in patients who have developed tolerance to opioids or other sedative.

Propofol infusions are also increasingly used for sedation in the ICU. Propofol causes a dose-dependent respiratory and circulatory depression, which can be generally minimized by limiting its use in the ICU to low-dose ranges of 15 to 50 mcg/kg/min. Propofol's principal advantage is that its effects usually dissipate within 1 hour after the infusion is stopped. Withdrawal is rare, but has been reported following prolonged infusion. Propofol infusion syndrome (PRIS) presents with cardiovascular instability, metabolic acidosis, hyperkalemia and rhabdomyolysis [41]. Etomidate was used in the past because of stable hemodynamic effects, but its adrenocortical suppressive effect has severely limited its use in ICU patients.

Dexmedetomidine (Precedex) infusion is used to provide sedation and relieve anxiety without causing respiratory depression. Its analgesic effects are mediated by alpha 2 adrenergic receptors in the brain stem at the pons, namely locus coeruleus nucleus. It is the main site for synthesis of brain norepinephrine, also described as LC-NA system (locus coeruleus-noradrenergic system). It has similar effects to clonidine, and is more potent, and its duration of action is shorter. It may result in bradycardia, hypotension and may cause depression, and it may enhance the effect of beta blockers.

ICU-related disorders

Sleep disorders in the intensive care unit

Sleep deprivation and insomnia are commonly encountered in modern ICUs. The natural circadian rhythm is altered, causing major disruptions in normal sleep patterns [16]. Severe persistent insomnia can have major implications on both recovery from surgery and the general health of the patient [17]. Sleep deprivation may be caused by internal as well as external factors. External factors include the noises, bright lights and alarms that are ubiquitous in the ICU environment and are equally disruptive to normal sleep cycles. The administration of benzodiazepines, such as alprazolam, triazolam, lorazepam, and non-benzodiazepines hypnotic agents such as zolpidem (ambien), zaleplon (sonata), or eszopiclone (lunesta) may be useful at night to help re-establish normal sleep patterns. However, pain must be adequately controlled before resorting to these agents.

Intensive care unit psychosis and psychosis-like states

Intensive care unit psychosis is a common cause of psychomotor agitation, confusion, restlessness, and even failure to cooperate with deep-breathing exercises and physical therapy ambulation in postoperative patients [18,19]. Psychosis can result from increased brain dopaminergic activity that may be caused by illness, medications, or pain. The psychotic patient cannot understand the nature of his or her own illness, the ICU environment, or the intent of medical providers. Primary management of psychosis involves treatment of the underlying cause and immediate control of psychomotor symptoms. Haloperidol, droperidol, or chlorpromazine in small doses are useful in the treatment psychotic states. Small doses of midazolam or propofol can also be very helpful in the initial treatment of patients with severe agitation. However, ICU psychosis must be differentiated from acute depression, which can mimic psychosis. Central anticholinergic syndrome also can present with symptoms that mimic psychosis. An accurate diagnosis is important because antipsychotic drugs used in the treatment of ICU psychosis can aggravate acute depression or the anticholinergic syndrome.

Depressive Illness in the intensive care unit

Depression is underdiagnosed in ICU patients and often presents as a sleep disorder. The inability of a patient to communicate makes the diagnosis even more difficult. The tricyclic antidepressant desipramine (norpramin), is a selective norepinephrine inhibitor. When used in small doses of 10mg-20 mg/day, it was found to be very effective in alleviating symptoms of depression with suicidal ideations in ICU settings [20-22]. Ketamine intravenously is also very useful in treatment-resistant depression with suicidal ideation. A derivative of ketamine known as esketamine (spravato) is administered nasally and is approved by FDA for acute depression with suicidal thoughts.

Central anticholinergic syndrome

Anticholinergic syndrome can be caused by anticholinergic medications such as atropine or scopolamine, some opioids, anesthetic agents, antihistamines, antiemetics, and sepsis [23-26]. Restlessness, delirium, confusion, and obtundation characterize this syndrome. It is typically seen in elderly patients. Antipsychotic medications will often worsen the anticholinergic symptoms. Physostigmine (0.03-0.04mg/kg) can quickly improve symptoms and is useful in making the diagnosis [37-39].

Post-traumatic stress disorders

Posttraumatic stress disorder is the development of characteristic symptoms after one or more traumatic events. These events involve experiences of intense fear, horror, and helplessness as a result of a stress or threat to one's physical integrity. The incidence of PTSD in ICU patients has recently been shown to be about 30%, with a range between 5% - 63% (Jackson et al., 2007). Patients who have suffered from adult respiratory distress syndrome are more prone to develop posttraumatic stress disorders [27-31]. This may be related to inadequate

pain relief or sedation while receiving mechanical ventilation in the ICU. It will be interesting to evaluate the effects of SARS-CoV2 on ICU patients as data become available. Post traumatic disorder not only affect the patient, it can affect the family members and relatives [40].

Acute withdrawal syndromes

Critically ill patients, especially those on ventilators who suffer from the adult respiratory distress syndrome, may require large doses of opioids and benzodiazepines. During weaning from these pharmacological agents, patients frequently experience withdrawal symptoms [32-36]. A recent study by Cammarano., *et al.* [36] shows that the frequency of withdrawal symptoms is as high as 32% with opiates and benzodiazepines. Withdrawal symptoms are often observed in mechanically ventilated adults who are in the ICU for more than 7 days. Younger patients and those with the adult respiratory distress syndrome tend to experience more withdrawal symptoms than elderly patients. Benzodiazepine withdrawal appears to be more serious than opioid withdrawal. Careful selection and dosing of sedatives accompanied by a planned, gradual weaning process and the appropriate use of antidepressants and antipsychotic agents can minimize withdrawal symptoms.

Conclusion

Appreciating, evaluating and understanding all the patient's evolving problems in the ICU is of utmost importance in achieving desirable outcomes. Maximizing meaningful human contact, effective pain, and ensuring adequate sleep are also essential to the care of ICU patients. Altered mental states such delirium, depression, psychosis, and the anticholinergic syndrome must be diagnosed and treated appropriately. Attention to the emotional and psychological needs of the ICU patients should be considered as important as their physical and physiological needs. Emphasis on individualized patient care is helpful for providers as well as for ICU patients.

Bibliography

1. Holland J., *et al.* "The ICU syndrome; Fact or fancy". *Psychiatric Medication* 4 (1973): 241-249.
2. Asbury AJ. "Patients' memories and reactions to intensive care". *Critical Care Ill* 1 (1985): 12-13.
3. Kehlet H. "Pain relief and modification of the stress response*". Critical Care Medicine Critical Care* 8 (1986): 49-75.
4. Phillips GD and Cousins MJ. "Neurological mechanisms of pain and the relationship of pain anxiety and sleep". *Critical Care Medicine Critical Care* 8 (1986): 21-48.
5. Campbell IT., *et al.* "Are circadian rhythms important in intensive care?" *Intensive and Critical Care Nursing* 1 (1986): 144-150.
6. Moore-Ede MC., *et al.* "Circadian timekeeping in health and disease. Part I. Basic properties of circadian pacemakers". *The New England Journal of Medicine* 309 (1983): 469-476.
7. Adam K and Oswald I. "Protein synthesis, bodily renewal and the sleep-wake cycle". *Clinical Science* 65 (1983): 561-567.
8. Baxter S. "Psychological problems of intensive care". *British Journal of Hospital Medicine* 11 (1974): 875-885.
9. Bowden P. "Psychiatric aspects of intensive care". in Tinker J, Rapin M (edITIONs): Care of the Critically Ill. Berlin, Germany, Springer-Verlag (1983): 787-797.
10. Strain JJ. "Psychological reactions to acute medical illness and critical care". *Critical Care Medicine* 6 (1978): 39-44.
11. Marks RM and Sacher EJ. "Undertreatment of medical inpatients with narcotic analgesics". *Annals of Internal Medicine* 78 (1973): 173-181.

12. Dasta JF., *et al.* "Pattern of prescribing and administering drugs for agitation and pain in a surgical intensive care unit". *Critical Care Medicine* 22 (1994): 974-980.

13. Cronin M and Redfern PA. "Psychiatry and post-operative pain complaints in surgical patients". *British Journal of Anaesthesia* 45 (1973): 879-886.

14. Tittle M and McMillian SC. "Pain and pain-related side effects in an ICU and on a surgical unit: Nurses' management". *The American Journal of Critical Care's* 3 (1994): 25-30.

15. Maxam-Moore VA., *et al.* "Analgesics for cardiac surgery patients in critical care: Describing current practice". *The American Journal of Critical Care's* 3 (1994): 31-39.

16. Aurell J and Elmqvist D. "Sleep in surgical intensive care unit". *British Medical Journal* 290 (1985): 1029-1032.

17. Adam K and Oswald I. "Sleep helps healing". *BMH* 289 (1984): 1400-1440.

18. Wollschlager CM., *et al.* "Common complications in critically ill patients". *Disease-a-Month* 34 (1988): 221-293.

19. Easton C and MacKenzie F. "Sensory-perceptual alterations: Delirium in the intensive care unit". *Heart Lung* 17 (1988): 229-237.

20. Bronheim HE., *et al.* "Depression in the intensive care unit". *Critical Care Medicine* 13 (1985): 985-988.

21. Brock-Utne JG., *et al.* "Psychiatric problems in intensive care". *Anaesthesia* 31 (1976): 380-384.

22. Dobb GJ and Murphy DF. "Sedation and analgesia during intensive care". *Journal of Clinical Anesthesiology* 3 (1985): 1055-1085.

23. Cook B and Spence AA. "Post-operative central anticholinergic syndrome". *European Journal of Anaesthesiology* 14 (1997): 1-2.

24. Rupreht J and Dworacek B. "The central anticholinergic syndrome in the postoperate period". in Nunn JF, Utting JE, Brown BR (editions): General Anaesthesia. London, UK, Butterworths (1989): 1141-1148.

25. Torline RL. "Central anticholinergic syndrome following reversal of neuromuscular blockade". *Anesthesiology Review* 20 (1993): 47-50.

26. Sun KO. "Central anticholinegic syndrome following reversal of neuromuscular blockade". *Anaesthesia and Intensive Care Medicine* 21L (1993): 363-365.

27. Horowitz MJ. "Stress-response syndromes. A review of posttraumatic stress and adjustment disorders". in Wilson JP, Raphael B (editions): International Handbook of Traumatic Stress Syndromes". New York, NY, Plenum (1993): 49-60.

28. Gersons BPR. "Post-traumatic stress disorder: The history of a recent concept". *British Journal of Psychiatry* 161 (1992): 742-748.

29. Davidson JRT and Foa EB. "Diagnostic issues in posttraumatic stress disorder: Considerations for the DSM-IV". *Journal of Abnormal Psychology* 100 (1991): 346-355.

30. Macleod AD and Maycock E. "Awareness during anesthesia and post traumatic stress disorder". *Anaesthesia and Intensive Care Medicine* 20 (1992): 378-382.

31. Schelling G., *et al.* "Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome". *Critical Care Medicine* 26 (1998): 651-659.

32. Hantson P., *et al.* "Withdrawal syndrome following midazolam infusion". *Intensive Care Medicine* 21 (1995): 190-191.

33. Shafer A., *et al.* "Use of fentanyl infusion in the intensive care unit: Tolerance to its anesthetic effects?" *Anesthesiology* 59 (1983): 245-248.

34. Buck M and Blumer J. "Opioids and other analgesics: Adverse effects in the intensive care unit". *Critical Care Clinics* 7 (1991): 615-637.

35. Katz R., *et al.* "Prospective study on the occurrence of withdrawal in critically ill children who receive fentanyl by continuous infusion". *Critical Care Medicine* 22 (1994): 763-767.

36. Cammarano WB., *et al.* "Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients". *Critical Care Medicine* 26 (1998): 676-684.

37. Gopinathan V. "Central anticholinergic syndrome - a forgotten entity". *British Journal of Anaesthesia* 101 (2008).

38. Katsanoulas K., *et al.* "Undiagnosed central anticholinergic system may lead to dangerous complications". *European Journal of Anaesthesiology* 16 (1999): 803-809.

39. Jackson JC., *et al.* "Post-traumatic stress disorder and post-traumatic stress symptoms following critical illness in medical intensive care unit patients: Assessing the magnitude of the *problem". Critical Care Medicine* 11 (2007): R27.

40. Azoulay E., *et al.* "Risk of post-traumatic stress symptoms in family members of intensive care unit patients". *American Journal of Respiratory and Critical Care Medicine* 171 (2005): 987-994.

41. Fudickar A., *et al.* "Propofol infusion syndrome in anaesthesia and intensive care medicine". *Current Opinion in Anesthesiology* 19.4 (2006): 404-410.

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