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Analysis of Multiple Routes of Analgesic Administration in the Immediate Postoperative Period: a 10-Year Experience

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Abstract

Purpose of Review An increasing amount of literature supports a multimodal approach to analgesic administration in the management of postoperative pain. The purpose of this study and review was to further evaluate the differences in efficacy in controlling immediate postoperative pain among the various routes of analgesia administration.

Recent Findings This study consisted of an analysis of the various routes of analgesic administration (parental, neuraxial, and oral/rectal) in 107,671 consecutive surgical cases performed over a 10-year period at Yale New Haven Hospital. This study included variables of postoperative pain score at initial request for analgesic, pain score at discharge, nausea and vomiting in the post-anesthesia care unit, and gender. The most common route of administration of analgesia in our study was via the parenteral route (29,962), and the least common route was the neuraxial route (1319). There was a significant decrease in pain scores at the time of discharge in all three groups relative to the pain score at first request for analgesia.

Summary Multimodal analgesia via various routes of administration targets numerous proponents of the nervous system with the intent to reduce the adverse side effects of the individual analgesics if given alone or as an additive to produce synergistic analgesia. Our study suggests that although all the routes investigated (parenteral, neuraxial (intrathecal/epidural), and per os or per rectum (PO/PR)) promote significant pain relief on discharge from the PACU, the group that received neuraxial analgesia reported the lowest incidence of nausea and vomiting.

Keywords Postoperative pain · Multimodal analgesia · Route of administration

Introduction

The management of postoperative pain holds critical value in the recovery of the patient. Both the International Association for the Study of Pain and the World Health Organization have acknowledged the relief of pain as a human right [1].

Studies have shown that inadequately managed postoperative pain can lead to protracted rehabilitation and complications [2]. Conversely, adequate management of pain relief leads to decreased hospital costs, greater patient satisfaction, and decreased hospital stays. The literature also indicates that acute pain that is poorly managed is associated with the progression to chronic pain and a decrease in quality of life [3]. Acute postoperative nausea, vomiting, and pain are the most common clinical complications following major ambulatory surgery. And although recent advancements in novel minimally invasive surgical techniques and modes of anesthesia administration have broadened the range of ambulatory surgery procedures [4, 5], adequate control of pain continues to be an issue in patient care. In fact, in Canada and the USA, approximately 70% of surgeries are conducted in the major ambulatory surgery setting and of these patients, up to 30% of subjects report moderate to severe pain within the first 24 h postoperatively despite being given analgesic treatment [6].

Patient satisfaction regarding in-hospital management of pain is scored via the Hospital Consumer Assessment of Health Providers and Systems (HCAHPS) scores. The lack of sufficient postoperative pain analgesia may stem from multiple reasons, including staff shortages, inadequate pain

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assessment tools, lack of education, and hesitation in administering analgesic drugs due to their associated complications [7]. The gold standard in self-assessment of pain by patients is done customarily after surgery in order to assess the efficacy of the management of pain. It is nationally recognized that within a 10-point pain scale, 1 represents no pain, whereas 10 represents the worst pain imaginable.

Postoperative pain can be managed using numerous routes, including neuraxial, per os or per rectum, and parenteral (regional, intravenous). An increasing amount of literature supports a multimodal approach that branches away from the traditional method of sole opioid administration with the objective to decrease adverse side effects of opioids including ileus and nausea, and to improve pain scores. Multimodal analgesia is the administration of a combination of various analgesics, including NSAIDs, local anesthetics, and opioids, which target pain via differing mechanisms resulting in synergistic analgesic effects, necessitating reduced doses of analgesics, and thereby decreased adverse side effects [8]. We conducted this study in order to assess the differences in efficacy among the various routes of analgesia administration in an attempt to further improve the management of pain in patients postoperatively.

Patient and Methods

The various routes of pain medication administration, parenteral, neuraxial, and oral/rectal, in 107,671 consecutive surgical cases that were performed over a 10-year period at the Yale New Haven Hospital were analyzed in this study. This was correlated with variables of postoperative pain score at initial request for analgesia, pain score at discharge, nausea and vomiting in the post-anesthesia care unit (PACU), and gender. A standardized survey collection form was utilized for the collection of prospective data that are expressed as percentage and *N*, 95% confidence intervals, and mean values. The association between categorical variables was tested with chi-square statistic. All statistical analyses were performed with SAS software, version 9.2 (Cary, NC), and a p value of less than 0.05 was considered statistically significant.

Results

A total of 107,671 patients were included in the analyses of this study (see Table 1). These patients were then subdivided into groups based on the route of administration of analgesia postoperatively into parenteral, neuraxial (intrathecal/epidural), and per os or per rectum (PO/PR). The most common route of administration of analgesia in our study was via the parenteral route, whereas the least common route of administration was the neuraxial route. A total of 29,962 patients received parenteral analgesia, 1319 received neuraxial neuralgia, and 8936 received analgesia PO or PR. There was a significant decrease in pain scores at the time of discharge in all three groups relative to the pain score at first request for analgesia. Among the 29,962 patients who received parenteral anesthesia, the median pain score at first request for analgesia was 7 (IQR 5–8), which decreased to a median score of 3 (IQR 2–4). Median pain scores decreased from 7 (IQR 5–10) to 2 (IQR 1–4) in the patients who received neuraxial analgesia, and from 5 (IQR 4–8) to 3 (IQR 2–4) in those who received PO or PR analgesia. The incidence of nausea and vomiting was highest in the group that was given parenteral medications, and least in those who received neuraxial blockade. A total of 56.3% of the parenteral group, 16.2% of the PO/PR group, and 1.8% of the neuraxial group reported nausea and vomiting. General anesthesia was used in 9.4% of the parenteral group, 8.4% of the PO/PR group, and 1.5% of the neuraxial group. Other methods of anesthesia were administered to the remaining subjects of the study.

Discussion

Neuraxial Analgesia

Neuraxial analgesia works by decreasing the afferent transmission of nociceptive signals in order to block sensitization of the central nervous system. The administration of neuraxial blocks includes intrathecal and epidural analgesia, which are used considerably in pelvic, thoracic, and abdominal surgery. Other techniques include regional, peripheral, and local nerve blocks, which target the nerve in the surgical field. Though neuraxial analgesia effectively decreases postoperative pain, potential complications include neuronal injury, which is a severe but rare neurological complication [9]. The absolute contraindications to neuraxial analgesia include infection at the injection site, coagulation defects, elevated intracranial pressure, spinal cord compression, and unstable spinal fracture [10].

Epidural analgesia is administered using a catheter that is placed into the epidural space either in the thoracic or lumbar spine. A continuous infusion of opioids with a local anesthetic agent is administered, thereby providing postoperative analgesia. Epidural catheter insertion can be challenging from a technical aspect—failure of sufficient analgesia is found in 32% of thoracic epidurals and 27% of lumbar epidurals despite appropriate catheter placement [11].

Intrathecal analgesia consists of administration of drugs directly into the intrathecal space via the CSF [12]. Drugs given intrathecally are roughly more potent by tenfold relative to those injected into the epidural space. As a result, volumes and doses of drugs administered are much lower [13]. The administration of local anesthetic (0.5% bupivacaine) and

Table 1 Routes of analgesia

	Route analgesia								
	Parenteral			Intrathecal/epidural			PO or PR		
	Yes (n = 29,962)	No (n = 71,916)	p value	Yes (n = 1319)	No (n = 100,559)	p value	Yes (n = 8936)	No (n = 92,942)	p value
Pain score at first request for analgesia	7 (5–8)	5 (2–4)	< 0.001	7 (5–10)	6 (5–8)	< 0.001	5 (4–8)	7 (5–8)	< 0.001
Pain score at discharge	3 (2–4)	1 (1–2)	< 0.001	2 (1–4)	2 (1–4)	0.8	3 (2–4)	2 (1–4)	< 0.001
Gender									
Male	31.6%	68.4%	< 0.001	1.2%	98.8%	0.027	8.9%	91.1%	0.033
Female	26.2%	73.8%		1.4%	98.6%		8.5%	91.5%	
Nausea and vomiting									
Yes	56.3%	27.9%	< 0.001	1.8%	1.3%	0.002	16.2%	8.3%	< 0.001
No	43.7%	72.1%		98.2%	98.7%		83.8%	91.7%	
Anesthesia									
General	9.4%	90.6%	< 0.001	1.5%	98.5	< 0.001	8.4%	91.6	< 0.001
Others	62.1%	37.9%		0.9%	99.1%		9.7%	90.3	

Data are presented as median (interquartile range) or percentage. Wilcoxon rank sum test or chi-square test was used

opioid intrathecally at induction of anesthesia provides suitable analgesia postoperatively for up to 24 h. The administration of analgesia intrathecally preoperatively takes a similar amount of time as placing an epidural, but does not require the careful management of postoperative care that is necessary when an epidural is placed for postoperative administration of analgesics [7].

Epidural anesthesia is commonly used to manage postoperative pain following major abdominal surgery. It has been found to decrease gastrointestinal, cardiovascular, and pulmonary morbidities, particularly in high-risk patients relative to systemic opioids [14–16]. The utilization of epidural analgesia in laparoscopic procedures including laparoscopic colorectal surgery and cholecystectomy has been limited due to equivocal benefits compared with systemic opioids [17]. Furthermore, epidural analgesia has a low but serious risk of adverse neurologic complications including the formation of hematoma or abscess, which can inflict permanent injury [18]. The risk of developing epidural hematomas is further increased when patients are on anticoagulant therapy, which is commonly administered postoperatively for pulmonary embolism prophylaxis. Other complications due to epidural anesthesia include dural punctures and the resulting headaches, hypotension, and improper placement requiring removal [19].

There have been numerous studies investigating the efficacy of epidural anesthesia relative to other routes of anesthesia administration. A study conducted by Shibasaki et al. [20] compared the efficacy of postoperative pain management post-laparoscopic gastrectomy between epidural anesthesia and celecoxib plus fentanyl therapy. It found that there were no significant differences in the severity of postoperative pain on postoperative day (POD) 0 or 1 between either of the groups. The total amount of rescue pain medications (acetaminophen, pentazocine, flurbiprofen) administered within the initial 7 days postoperatively did not differ between the two groups ($p < 0.05$). By POD 2 through POD 7, patients in the group receiving fentanyl and celecoxib reported a significantly lower degree of pain compared with patients given epidural analgesia. The study did not find any significant differences in postoperative pulmonary or cardiovascular complications, or differences in perioperative vital signs, suggesting that epidural anesthesia failed to provide a significantly more efficacious mode of postoperative pain relief relative to celecoxib plus fentanyl therapy.

In a study conducted by a Cochrane database review including nine randomized controlled trials matching continuous epidural analgesia (CEA) against IV patient-controlled analgesia (PCA), it was demonstrated that within the initial 72 h following abdominal surgery, CEA provided more effective pain relief [21]. However, patients who received CEA also reported a greater incidence of pruritus relative to the opioid group. There were no significant differences in adverse events and hospital stay between the two groups. A consequent meta-analysis of randomized controlled trials that compared CEA and IV PCA in patients who underwent colorectal surgery found consistent results [22]. There was a significant decrease in ileus and postoperative pain in the group that received CEA. On the other hand, this group also reported a greater incidence of adverse side effects including hypotension, pruritus, and urinary retention. A patient-controlled epidural pump can also be provided, through which an opioid and local anesthetic combination can be administered, which has

the advantage of effectively decreasing the adverse side effects, as well as the dosage requirements for each drug given [23].

A recent observational study demonstrated that single-dose administration of opioid intrathecally then providing IV PCA resulted in superior pain relief compared with patients who were given CEA following colorectal surgery [24]. Additionally, advantages in this group included decreased hospital stay and time that it took for patients to regain mobility. Another randomized controlled trial was conducted in order to assess the efficacy in pain control between IV PCA, CEA, and intrathecal analgesia in patients who underwent laparoscopic colorectal surgery, and found that pain scores were significantly higher in the IV PCA group relative to the other two groups. The study also found that the duration of hospital stay, duration of nausea, and return of bowel function were greater in the CEA group in comparison to the other groups [25].

Complications of Neuraxial Analgesia

Despite the numerous advantages to neuraxial analgesia, there are several complications that a clinician must be mindful of. Meningitis, infection surrounding the catheter, and epidural abscesses are some serious risks that can be introduced through this route of administration. Infections can develop at the site of entry, along the path of the tunneled catheter, and within the epidural space [13]. The incidence of meningitis following placement of an intrathecal pump is 3% [26]. It has been proposed that the placement of epidurals decreases the incidence of meningitis, but the rate of infection has been comparable [27]. Another potential complication arises from the trauma to blood vessels in the epidural space during the insertion or removal of the catheter. In particular, hematomas are at greater risk of forming in patients on antiplatelet medication, anticoagulants, and antifibrinolytics [13].

Opioid Analgesia

Notwithstanding countless years of advancements in the management of pain, the core of the majority of pain management continues to remain centered around opioids. Opioids can be administered through various routes, including parenteral, neuraxial, transdermal, rectal, and oral routes. Via the intravenous route, the most frequently used opioids utilized for postoperative pain include fentanyl, morphine, and hydromorphone. Hydromorphone and fentanyl are synthetic morphine derivatives that have shorter half-lives, decreased onset of action, and greater potency relative to morphine. Morphine continues to be the standard selection of opioid and is commonly used. Its onset of action is rapid, with its effect peaking at 1 to 2 h [7].

Given via neuraxial routes, opioids provide significant analgesia due to direct uptake of the drug into the CSF and spinal cord. They inhibit transmission of pain signals by binding to presynaptic and postsynaptic receptors in the brainstem and spinal cord. Lipophilic opioids, including sufentanil and fentanyl, preferentially travel into the white matter, whereas hydrophilic opioids including hydromorphone and morphine preferentially travel into the gray matter. Lipophilic drugs are associated with a more rapid onset of action, though of shorter duration. They are therefore more effective when given via continuous infusion. On the other hand, hydrophilic drugs have a delayed onset of action and a greater half-life in the CSF [13].

The common adverse side effects of opioid therapy are the limiting factor in their widespread use clinically. The most critical side effect is respiratory depression, which could progress to hypoxia and respiratory arrest. This necessitates routine monitoring of oxygen saturation and respiration is crucial in patients who are given opioids in the postoperative period. Other common adverse side effects include pruritus, nausea and vomiting, ileus, and constipation [28]. The prolonged use of opioid therapy also presents the issue of addiction and dependence. When the patient is able to tolerate oral intake, opioids in the oral form can be started and given following discharge from the hospital [7]. The choice of drug administered is based on the clinician's familiarity with the drug, clinical studies of efficacy, and local drug availability [13].

Oxycodone

Oxycodone is a selective agonist of the μ-opioid receptor, with studies that also suggest activity on the κ-opioid receptor [29–31]. The drug has three pharmacologically active metabolites: oxymorphone, noroxycodone, and noroxymorphone, of which the parent drug seems to be the source of the analgesia [32]. The bioavailability of oxycodone depends on the route of administration, ranging from less than 20% if given sublingually, to approximately 60–80% if given orally [29, 33]. Oxycodone given intravenously may offer particular advantages to giving other opioids intravenously for the management of postoperative pain. IV oxycodone is becoming more commonly used for the management of pain postoperatively, especially due to its rapid onset of action and its utilization in the immediate postoperative period [34].

Several studies have investigated the analgesic efficacy of oxycodone compared with other opioids. A randomized study of patients undergoing laparoscopic cholecystectomy found that patients given IV oxycodone at the end of anesthesia reported significantly lower abdominal pain intensity on entering the PACU at 30, 60, and 90 min compared with patients who received IV fentanyl [35]. When comparing the outcomes of patients who received IV oxycodone or IV morphine, another study found that the patients who received oxycodone were given significantly less PCA. Although the

adverse effects, including pruritus, nausea, and vomiting, were comparable between the two groups, the patients on oxycodone demonstrated significantly decreased sedation in the initial 24 h post-surgery [36]. On the other hand, a randomized study conducted on 50 patients undergoing major surgery found that patients given PCA morphine or PCA oxycodone postoperatively reported comparable rates of adverse effects and analgesic efficacy [37].

Fentanyl

Fentanyl is a synthetic low molecular weight opioid, with high analgesic potency when given intravenously. Given intravenously, it is more potent than morphine by 50- to 100-fold [38]. It is also effective given transdermally due to its high lipid solubility and small molecular structure [39]. The fentanyl iontophoretic transdermal system (ITS) is a self-programmed delivery method that is easily applied and designed for acute and chronic pain management, which is useful in patients postoperatively [40]. The patches deliver fentanyl through the skin at a constant rate, though it is pharmacokinetically similar to IV fentanyl [39]. The most common side effects of fentanyl patches include pruritus, edema, discoloration, and erythema [41].

Studies have shown that fentanyl administered via PCA is comparable in analgesia postoperatively compared with fentanyl given through ITS [41–43]. Trials have also demonstrated that fentanyl ITS is at least as effective as the standard morphine PCA regimen in non-drug-dependent patients [44–46]. The advantage of the PCA regimen is that the frequency of doses given is determined by the patient as needed, which decreases the possibility of overdose [40]. A meta-analysis of 15 randomized controlled studies revealed that patients given PCA postoperatively reported significantly better pain relief compared with those who were given analgesia via the intramuscular route, without greater adverse effects [47].

Morphine

Epidural Morphine

Morphine was the initial opioid that was approved for spinal administration by the US Food and Drugs Administration (FDA) [48]. It is the most commonly used opioid for epidurals and is consequently commonly compared with other spinal drugs when studying analgesic efficacy [49•]. Morphine administered via epidurals has proven to have superior analgesic efficacy compared with morphine given systemically for the management of postoperative pain [49•, 50, 51]. Given that a single injection of epidural morphine lasts less than 24 h, several techniques are utilized in order to prolong its effects, including continuous epidural infusions, PCA pumps, and frequent injection, although these techniques can be inconvenient and expensive [52].

In response to the potential complications from indwelling epidural catheters, especially in anticoagulated patients, the FDA approved the utilization of liposome-based extended release epidural morphine (EREM) in 2004 [49•]. EREM was developed for single-dose use via the epidural route on the lumbar level. It effectively prolonged the duration of analgesia to 48 h following single-dose injection, and also delays the peak concentration in the cerebrospinal fluid to 3 h following administration [53]. Another benefit to EREM is that there are no catheter-related issues [48].

Intrathecal Morphine

Administration of opioids intrathecally is an appealing technique because it is injected directly into the CSF, in proximity to structures of the central nervous system, the site of action [49•]. Once injected, the opioid makes its way toward the head through the cerebrospinal fluid and undergoes spinal diffusion, thereby binding to specific receptors in the gray matter and nonspecific receptors in the white matter [54]. Lipophilic opioids, including morphine, diffuse across the blood–brain barrier gradually, bind to the epidural fat with less affinity, have delayed reuptake in the plasma, and maintain higher concentrations in the CSF for prolonged periods. Consequently, morphine has a slow onset of action and a gradual spread, resulting in an extensive region of analgesia around the site of injection, a prolonged duration of action ranging from 18 to 24 h, and delayed respiratory depression [55].

Non-opioid Analgesia

NSAIDs

Another important consideration in tailoring postoperative management of pain is the use of non-opioid analgesia, also referred to as opioid-sparing methods. Non-steroidal anti-inflammatory agents (NSAIDs) are effective in decreasing the quantity of opioids given to the patient, thereby minimizing the aforementioned side effects [56]. NSAIDs work via inhibition of cyclooxygenase (COX), thus blocking the synthesis of prostaglandins, effectively sustaining an anti-inflammatory response. Arachidonic acid is oxidized via cyclooxygenase catalyzation, producing cyclic prostaglandins [57].

They are classified based on their selectivity of the COX isoenzymes, and are valuable in managing mild to moderate levels of pain. COX-1 and COX-2 are two enzymes that are comparable structurally, but contain two integral differences at their active site in amino acid sequence [58]. Whereas COX-1 is involved in homeostasis, COX-2 participates in pathways of inflammation and pain [59]. Specifically, COX-1 enzymes are responsible for maintaining the gastric mucosa and kidney

function, and permitting normal aggregation of platelets [60]. The risk of bleeding increases on this medication, thereby necessitating an appropriate review of the patient's comorbidities [7]. Serious adverse effects aside from surgical bleeding [61•, 62] that have been reported include renal impairment [63], GI bleeding [61•, 62], and cardiovascular events [63].

Acetaminophen

Acetaminophen is a centrally acting anesthetic that does not provide anti-inflammatory effects peripherally. It is commonly given in oral form for acute pain management. Systematic reviews of randomized controlled trials have successfully demonstrated its efficacy in the management of acute pain [64]. It is also a widely used ingredient in numerous combination pain medications given orally. It is therefore important to notify the patient that their daily intake should not exceed 4000 mg, in order to avoid hepatotoxicity. Until recently, the inability to administer oral analgesics immediately following surgery had limited its usefulness in treating immediate postoperative pain. Furthermore, acetaminophen has a slow onset of analgesia.

However, paracetamol, which is a stable IV form of acetaminophen, is now available. The intravenous formulation was approved in 2010 for mild to moderate pain, moderate to severe pain alongside adjunctive opioids, and fever [65•]. The major benefit of this drug over the other NSAIDs includes its safety profile in the use of patients with asthma and peptic ulcers, as well as its lack of modification of platelet function [7]. Administration of paracetamol intravenously has also been associated with opioid-sparing effects, thereby providing another advantage to its usage [66]. A study found that when paracetamol, COX-2 inhibitors, or NSAIDs were given with PCA morphine following surgery, there was reduction in the 24-h consumption of morphine, and a decrease in the incidence of adverse side effects from the morphine [66]. There were no significant differences between the paracetamol, COX-2 inhibitors, or NSAIDs. Notably, a systematic review by Ong et al. [67] found that, based on 21 studies, the use of paracetamol in combination with other NSAIDs yielded greater efficacy than with the treatment of paracetamol alone.

Ketamine

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that is used for induction particularly in pediatric patients, with growing interest in its use as an analgesic for the management of acute pain. It is thought to provide postoperative pain relief via inhibition of the sensitization of the nociceptive pathway in the central nervous system [68]. A meta-analysis and systematic review of the effects of perioperative intravenous ketamine found that it had an opioid-sparing effect, especially with procedures associated with greater postoperative pain, such as thoracic, orthopedic, and abdominal surgeries. The administration of ketamine was also associated with reduced postoperative pain scores in 37.5% of studies at early intervals (ranging from 30 min to 4 h) and 25% of studies at extended intervals (ranging from 24 to 72 h). Despite this efficacy in pain management and decreased risk of postoperative nausea and vomiting, the study found that ketamine elevated the risk of neuropsychiatric effects such as hallucinations [69], which is managed with a perioperative dose of benzodiazepine [70]. Other adverse effects include dysphoria, diplopia, and sedation [71].

Ibuprofen

In 2009, an intravenous formulation of ibuprofen was approved for mild to moderate pain, for moderate to severe pain in conjunction with opioids, and for fever reduction [65•]. A recent review of the clinical trials studying the tolerability and efficacy of intravenous ibuprofen found that 800 mg given every 6 h postoperatively was effective as a morphine adjunct and as a morphine-sparing substance [72]. In addition, the review determined that the common adverse side effects of intravenous ibuprofen included nausea, vomiting, dizziness, headache, hemorrhage, and urinary retention but that the agent was generally well tolerated [72].

Conclusion

Multimodal analgesia using various routes of administration targets numerous proponents of the nervous system with the intent to reduce the adverse side effects of the individual analgesics if given alone or as an additive to produce synergistic analgesia. The results of our study demonstrated that although all the routes investigated, parenteral, neuraxial (intrathecal/epidural), and per os or per rectum (PO/PR), promote significant pain relief on discharge from the PACU, the group that received neuraxial analgesia reported the lowest incidence of nausea and vomiting. Numerous factors are essential to consider when deciding the route of analgesia in the postoperative setting, making it challenging to standardize. The factors that need to be considered include prior analgesic use, medical condition, age, surgical procedure, anxiety, and allergies. Studies that further investigate how different routes of analgesia affect pain outcomes and elucidation on the patients who would best benefit from which form of analgesia are warranted.

Given the enormity of the size of data, specific data points including specific routes of administration, drugs used, and procedures performed were not collected. This is a limitation of our study, and the authors propose that future studies focus on these details to further elucidate the efficacy of different routes, and their application to managing pain in the postoperative period.

Compliance with Ethical Standards

Conflict of Interest Nalini Vadivelu, Alice M Kai, Feng Dai, and Susan Dabu-Bondoc declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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