A Review of Anesthetic Effects on Renal Function: Potential Organ Protection

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Keywords

Anesthetic drugs · Ischemia-reperfusion injury · Volatile anesthetics · Organ protection · Transplant · Intravenous anesthetics · Lipid emulsion · Propofol · Cardioprotection · Renal protection

Abstract

Background: Renal protection is a critical concept for anesthesiologists, nephrologists, and urologists, since anesthesia and renal function are highly interconnected and can potentially interfere with one another. Therefore, a comprehensive understanding of anesthetic drugs and their effects on renal function remains fundamental to the success of renal surgeries, especially transplant procedures. Some experimental studies have shown that some anesthetics provide protection against renal ischemia/reperfusion (IR) injury, but there is limited clinical evidence. **Summary:** The effects of anesthetic drugs on renal failure are particularly important in the context of kidney transplantation, since the conditions of preservation following removal profoundly influence the recovery of organ function. Currently, preservation procedures are typically based on the usage of a cold-storage solu-

tion. Some anesthetic drugs induce anti-inflammatory, anti-necrotic, and anti-apoptotic effects. A more thorough understanding of anesthetic effects on renal function can present a novel approach for developing organ-protective strategies. The aim of this review is to discuss the effects of different anesthetic drugs on renal function, with particular focus on IR injury. Many studies have demonstrated the organ-protective effects of some anesthetic drugs, specifically propofol, which indicate the potential of some anesthetics to introduce novel organ protective targets. This is not surprising, since lipid emulsions are major components of propofol, which accumulating data show provide organ protective effects against IR injury. **Key Messages:** Thorough understanding of the interaction between anesthetic drugs and renal function remains fundamental to the delivery of safe perioperative care and to optimizing outcomes after renal surgeries, particularly transplant procedures. Anesthetics can be repurposed for organ protection with more information about their effects, especially during transplant procedures. Here, we review the effects of different anesthetic drugs – specifically those that contain lipids in their structure, with special reference to IR injury.

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Introduction

Renal ischemia/reperfusion (IR) injury is a leading cause of preoperative acute kidney injury (AKI), which frequently complicates major vascular, cardiac, transplant, and liver surgeries [1]. AKI has been shown to occur after some major surgeries, raising questions regarding the role of the operative procedures – including the administration of anesthesia and its effects on renal function [1].

There is contradictory evidence regarding the effects of anesthetics on renal function. Some studies have shown that the administration of some types of anesthesia during surgery, as well as surgical stress itself, can affect renal function. Indirect effects are more pronounced than the direct effects [2]. However, other studies have shown that some anesthetic drugs induce anti-inflammatory, anti-necrotic, and anti-apoptotic effects that protect against AKI [3]. This raises several questions, including: Can anesthetics attenuate or prevent renal IR injury? What are the possible mechanisms? How does the anesthetic technique influence patient outcomes after renal transplantation? Can we repurpose them as organ-protective agents?

Identifying appropriate anesthetic technique for renal procedures, especially transplantations, is vital (Table 1). In particular, novel interventions that protect against IR injury are needed to improve early graft function after kidney transplantation. Available general and local anesthetics, including third generation inhaled anesthetics, propofol, and amide-class local anesthetics, are effective and safe with a low incidence of side effects. Anesthetics seem to exhibit an organ-protective potential via multiple different mechanisms, including reducing IR injury (Fig. 1) [4]. Some researchers propose that these anesthetics prevent the uncontrolled opening of the mitochondrial permeability transition pore after ischemia, which leads to the release of pro-apoptotic factors and necrotic cell death [5]. In particular, propofol, a widely used anesthetic, has shown potential as a novel organ-protective agent through its efficient membrane-targeted and cytoprotective effects [4]. This is not surprising since lipid emulsions are major components of propofol, which accumulating data show provide organ protective effects against IR injury in many organs, such as the heart, kidney, liver, and intestines [6–13].

In this review, we summarize the research history on the effects of anesthetic drugs on kidney function, including cellular mechanisms of anesthetic-mediated protection in different organs (Table 2).

General Anesthesia

Volatile Anesthetics

Volatile anesthetics are administered to many patients subjected to general anesthesia and are an integral part of the perioperative period. Methoxyflurane was the first nonflammable halogenated volatile anesthetic gas synthesized [3]. Methoxyflurane caused dose-dependent abnormalities post-surgery, including vasopressin-resistant polyuria, serum hyperosmolality, hypernatremia, increased concentrations of serum urea nitrogen and inorganic fluoride, and decreased urinary potassium, sodium, osmolality, and urea nitrogen concentrations, with clinical toxicity at dosages greater than 90 $\mu\text{mol/L}$ [14]. Consequently, nephrotoxicity induced by methoxyflurane was generalized to all halogenated anesthetics. However, most third-generation inhaled anesthetics are effective and safe [4].

Fluorinated anesthetics, specifically sevoflurane and enflurane, did not cause deterioration of postoperative renal function in patients with preexisting renal issues [15]; none of the patients needed dialysis or had permanent deterioration of renal insufficiency. Furthermore, both animal and human studies have demonstrated that neither the duration of systemic fluoride exposure nor the fluoride peak values corresponded to anesthetic nephrotoxicity [3]. In fact, the metabolism of enflurane to inorganic fluoride during and after surgery did not cause a clinically significant level of renal disease or dysfunction [16].

Accumulating data show protective effects of some volatile anesthetic drugs against IR injury [17, 18]. In a study analyzing data from the past 15 years, pre-injury administration of a volatile anesthetic was shown to decrease the impact of IR injury on the heart, brain, and kidney [19]. Other data demonstrated that volatile agents administered shortly after injury can decrease IR injury [20].

Additionally, Darwin's theory of evolution led to the concept of preconditioning, a mechanism in which brief sublethal periods of ischemia provide protection from a subsequent lethal episode of ischemia and mitigate the effect of IR [21]. Subsequently, the organism or the tissue will acquire an "injury-resistant" phenotype for a certain period [22]. Interestingly, brief periods of ischemia at the onset of reperfusion are associated with cardioprotection, leading to a decrease in myocardial infarction size [23]. Similarly, isoflurane has been shown to improve remodeling after coronary artery occlusion in rats [24]. Preconditioning is now a well-established property of volatile

Table 1. Overview of common anesthetic agents with their primary physiological and adverse effects

Drug	Action	Adverse effects
<i>Volatile anesthetics</i>		
Methoxyflurane	Analgesic	Respiratory and cardiovascular system depression, renal damage no longer available for use in the United States
Sevoflurane	Anesthetic	Raises intracranial pressure
Enflurane	Anesthetic	Increased risk of seizure activity, malignant hyperthermia
Isoflurane	Anesthetic	Moderate to severe airway irritability if used as an induction agent
<i>Intravenous anesthetics</i>		
Ketamine	Anesthetic Analgesic	Psychomimetic effects post-surgery
Dexmedetomidine	Anesthetic Analgesic	Use with caution in patients with preexisting cardiac conduction defects, bradycardia, hypovolemia
Propofol	Anesthetic	Respiratory and cardiovascular system depression
<i>Regional anesthetics</i>		
Bupivacaine	Analgesic	Cardiotoxicity
Lidocaine	Analgesic	

anesthetics, specifically of sevoflurane; these anesthetics are recommended as the agents of choice by the American Heart Association for high-risk patients. Preconditioning and postconditioning with sevoflurane exert a significant protective effect against IR injury in the rat lung transplantation model [25].

Other volatile anesthetics exhibit promising post-conditioning properties after cardiac surgery. At the basic level, the myocardial protective effects of sevoflurane involve apoptotic mRNA inhibition, neuromodulation, cytokine/inflammation modulation, redox-sensitive pathways, endothelial preservation, ion channels, and notch signaling pathways [26]. These findings open a new field of investigation for potential therapies aimed to diminish secondary organ injury, as well as transplants. However, more studies are required to assess the magnitude of collateral protection of other organs.

Additionally, researchers have looked at the possibility of adding volatile anesthetics to preservation solutions for renal transplantations. Such anesthetic management aims to maintain the optimum perfusion pressure of the renal allograft in order to preserve its function. Both sevoflurane and enflurane have been shown to undergo biodegradation into inorganic fluoride. Evidence of renal concentrating ability and renal tubular injury with transient impairment was found in patients who received sevoflurane and enflurane [27], as a serum fluoride concentration of 50 $\mu\text{mol/L}$ is the peak nephrotoxicity value.

Furthermore, sevoflurane can impair kidney function; the inorganic fluoride ions resulting from its defluorination and the production of compound A from the reaction with carbon dioxide absorbent have been associated with nephrotoxicity [28, 29]. Fluoride levels following the administration of isoflurane or halothane increase by 3–5 and 1–2 $\mu\text{mol/L}$, respectively, causing the risk of nephrotoxicity to be relatively improbable. Comparatively, desflurane's resistance to biodegradation allows even prolonged exposure to be associated with normal renal function [28]. In a recent study, researchers stored porcine kidneys in the preservation solution Celsior, which was saturated with argon or xenon. Argon-Celsior showed promise in renal transplant preservation by improving early functional recovery, graft quality, and survival, in comparison to Xenon-Celsior [30].

Recent studies have shown that volatile anesthetics provide protective effects during and after ischemic and inflammatory conditions that occur in the perioperative period by modulating IR injury and inflammation [3, 15, 16, 31]. Researchers found that isoflurane provides preconditioning renoprotective effects through anti-inflammatory and anti-apoptotic actions in a rat model [32]. Isoflurane may be protecting against renal tubular necrosis and inflammation by inducing renal tubular CD73 and adenosine generation, which is dependent on transforming growth factor-beta 1 [33]. Similarly, sevoflurane pretreatment enhanced hypoxia-inducible factor-2 α ex-

Fig. 1. Hypothesized mechanisms for protective effects of anesthetics.

pression in a mouse model of renal IR injury [34]. Another study showed that xenon protects against AKI by activating miR-21 target signaling pathways [35].

Additionally, a recent study simulating liver transplantation in rats investigated the mechanisms by which volatile anesthetics yield their organ protective effects, comparing the protective and antioxidant properties of sevoflurane and isoflurane [36]. It was found that sevoflurane had significantly better protective and antioxidant effects during both cold preservation and the early phases of organ reperfusion in comparison to isoflurane, suggesting the differential protective effects of common volatile anesthetics [36].

There is significant clinical evidence for volatile anesthetic-mediated organ protection. A recent study showed

that sevoflurane preconditioning significantly lessened the postoperative rise of transaminase levels in patients undergoing liver resection [37]. Furthermore, a short period of sevoflurane preconditioning in patients undergoing coronary artery bypass graft surgery was shown to significantly decrease both the release of a myocardial contractile dysfunction marker and the levels of plasma cystatin C concentrations [38]. These findings suggest that sevoflurane causes improvements in renal and cardiac function following major surgery. Additionally, a recent study suggested that during the early postoperative period following kidney transplantation, the estimated glomerular filtration rate improves significantly when living donors are anesthetized with a volatile anesthetic, as compared to with propofol [39]. The protective effects

Table 2. Proposed interactions and mechanisms of anesthetics

Drug	Proposed interactions
<i>Volatile anesthetics</i>	
Methoxyflurane	Nephrotoxicity [14]
Sevoflurane	No deterioration of renal function [15] Protective effect against IR injury [24] Nephrotoxicity due to production of inorganic fluoride ions and Compound A Preconditioning renoprotective effects [30]
Enflurane	No deterioration of renal function [15]
Isoflurane	Preconditioning renoprotective effects [28] Protected against renal tubular necrosis and inflammation by inducing renal tubular CD73 and adenosine generation [29]
<i>Intravenous anesthetics</i>	
Ketamine	Ameliorated the up-regulation of inflammatory pathways and reduction of metabolism caused by hypoxia [33]
Dexmedetomidine	Inhibited oxidative stress and inflammation [53]
Propofol	Reduced renal IR injury in rat model [40] Significantly reduced the incidence and severity of AKI in comparison to sevoflurane [48] and midazolam [49] Pretreatment prevented decrease in renal function and an increase in tubular apoptosis by inhibiting oxidative stress [42] Pretreatment protected cells against apoptosis induced by IR [46] Modulated systemic inflammation from IR by decreasing expression of nuclear factor- κ B [43] Mitigated renal IR injury via heme oxygenase-1 expression induction [44] Attenuated post-AOLT AKI via inhibition of Cx32 function [63] Promising renoprotective agent in renal transplantation [54]
<i>Regional anesthetics</i>	
Bupivacaine	Lower toxicity for the recipient and renal allografts during renal transplantation [57]
Lidocaine	Lower toxicity for the recipient and renal allografts during renal transplantation [57] Protection against IR injury via miRNA dysregulation prevention [60]

of volatile anesthetics were also evaluated in a recent study that investigated the mechanisms of IR injury, and identified one such mechanism as intracellular calcium overload. It was suggested that such anesthetics may protect the myocardium from IR injury by altering myocardial calcium fluxes, preserving myocardial energetics, and protecting the region from reactive oxygen species injury [40]. The relatively higher efficiency of enflurane and halothane in comparison to isoflurane regarding these effects has been explained by their effect on myocardial cells: halothane and enflurane primarily decrease intracellular calcium levels by directly acting on the sarcoplasmic reticulum, while isoflurane only decreases transsarcolemmal calcium entry (Fig. 1) [40].

Recently, various studies have shown the protective effects of volatile anesthetics in terms of renal IR injury.

One study determined that volatile anesthetics, such as isoflurane, provide IR injury protection by attenuating both inflammation and necrosis [41]. Another study showed that preconditioning with xenon had a protective effect by preventing renal IR injury from progressing to AKI due to its natural induction of hypoxia-inducible factor, thus yielding potentially important clinical applications [42]. Furthermore, another study investigating histological tubular cell damage in a rabbit model found that desflurane preconditioning reduced renal IR injury via its protective effect on the kidneys [43].

Although some volatile anesthetics attenuate AKI, multiple studies have shown that propofol, an intravenous anesthetic with anti-inflammatory properties, may attenuate AKI more effectively.

Intravenous Anesthetics

Renal IR injury is a risk factor for acute renal failure and delayed graft function. Pathogenic factors for renal IR include, but are not limited to, the following: oxidative stress, inflammation, cellular necrosis, and apoptosis [44]. Some anesthetic drugs induce anti-inflammatory, anti-necrotic, and anti-apoptotic effects through different mechanisms [3]. In a recent study, researchers intravenously administered ketamine into fetal sheep before inducing hypoxia. Ketamine ameliorated the upregulation of inflammatory pathways and reduction of metabolism caused by hypoxia [45]. Furthermore, thiopental pretreatment reduced renal IR injury induced by free radicals [46, 47]. Reinforcing this finding, dexmedetomidine has been shown to decrease brain IR injury and inhibit nuclear factor- κ B and intercellular adhesion molecule 1 expression through the inhibition of oxidative stress and inflammation, which are pathogenic factors of IR injury [48].

However, the majority of research studies have focused on the non-anesthetic effects of propofol, such as its antioxidant, immunomodulatory, analgesic, and neuroprotective effects [47]. Propofol has been shown to have protective effects against IR injury in multiple organs, including the heart, kidneys, liver, and intestines [6–13, 49–52].

The antioxidant abilities of propofol significantly reduced IR injury in a rat model of renal IR [53]. Researchers have shown that pretreatment with propofol attenuated the characteristic decrease in renal function and an increase in tubular apoptosis in male rat kidneys subjected to IR. Propofol protected cells from apoptosis by inhibiting oxidative stress and the corresponding downstream pathways, such as mitochondrial stress [54]. Propofol may counteract oxidative stress by lowering the formation of F(2)-isoprostane, a marker of oxidative stress, during transplantation and post-surgery [55]. Propofol also modulates systemic inflammation resulting from IR by decreasing the expression of nuclear factor- κ B, a nuclear transcription factor that plays a key role in oxidative stress (Fig. 1) [56]. Propofol may also induce heme oxygenase-1 expression in order to mitigate renal IR injury [57]. Furthermore, propofol can also induce protection against renal IR injury aggravated by hyperglycemia through its antioxidant abilities [58]. In comparison to etomidate, propofol significantly attenuated tubular damage after reperfusion in hyperglycemic rats. It also preserved superoxide dismutase levels and attenuated post-reperfusion increases in levels of myeloperoxidase, interleukin-1 β , tumor necrosis factor- α , production

of inducible nitric oxide synthase, and phosphorylation of inhibitor of κ B and nuclear factor- κ B [58].

Propofol may protect cells against apoptosis induced by IR through a preconditioning effect. In one study, propofol attenuated IR injury in LLC-PK1 cells when presented either 1 or 24 h before IR or during the recovery period but not when it was added only during ischemia. This effect may have been partially mediated by K_{ATP} channels [59]. In addition, propofol pretreatment may modulate bone morphogenetic protein 2 expression to reduce renal oxidative injury and facilitate repair following IR injury [60].

In a comparison between patients receiving propofol or sevoflurane during cardiopulmonary bypass, propofol significantly reduced the incidence and severity of AKI (which was defined using the AKI network criteria as an absolute increase in serum creatinine of 0.3 mg/dL, an increase $\geq 150\%$ from the baseline value, or as a urine output of <0.5 mL/kg/h for >6 h within 48 h postoperative) in comparison to sevoflurane [61]. This suggests that propofol may be a better renoprotective agent for cardiopulmonary bypass than sevoflurane. No relevant clinical complications occurred with either anesthetic method, and other postoperative outcomes (such as intensive care unit [ICU] stay and in-hospital mortality) were similar between the 2 groups. AKI that occurred in patients who received propofol was confined to the lowest stage of the AKI Network criteria, while AKI that occurred in patients who received sevoflurane varied across the disease spectrum. In fact, significantly more patients receiving sevoflurane displayed severe renal dysfunction and required dialysis. Measured perioperative changes in serum biomarkers of renal injury and inflammatory mediators, and the occurrence of postoperative complications contributed to the clinical evaluation of patient outcomes. C-reactive protein, creatine kinase-MB, and neutrophil counts were measured pre- and postoperatively, and interleukin-1, interleukin-6, and tumor necrosis factor- α levels were assessed to evaluate the degree of inflammation and AKI [61]. In another study, patients treated with propofol had better ICU survival than those treated with benzodiazepine. The outcomes for patients in the ICU that were exclusively treated with propofol or midazolam were compared for the first 48 h. Patients treated with propofol had a lower risk of AKI, fluid-related complications, and less need for RRT compared with midazolam [62].

It has been suggested that reperfusion-induced enhancement of the connexin32 (Cx32) gap junction plays an important role in mediating AKI post-liver transplan-

tation. In one study, male rats underwent autologous liver transplantation (AOLT) with or without selective Cx32 inhibitor, 20-amino-ethoxydiphenyl, or propofol. AOLT significantly increased renal Cx32 protein expression, gap junction formation, and oxidative stress, and it impaired renal function. Propofol inhibited Cx32 function while attenuating post-AOLT AKI [63]. Another study suggested that propofol exerts a renoprotective effect against AKI after orthotopic liver autotransplantation through the upregulation of the nuclear factor, erythroid 2-related factor 2, a regulator of the cellular-defense response protection against oxidative injury [64]. A recent study found that propofol protects against hepatic IR injury through the regulation of mitogen-activated protein kinase 6 expression by miR-133a-5p [65]. There is extensive supporting data regarding the protective effects of lipid emulsions against IR injury [6–13]. Considering the presence of lipids in propofol, this could provide new insights into organ-protective targets.

Additionally, researchers have evaluated the effectiveness of propofol in preservation solution in a porcine autotransplantation model after 45 min of ischemia. Their results demonstrated that propofol is a promising renoprotective agent that may attenuate hypothermic and ischemic AKI in renal transplantation through its antioxidant effects [66]. This mechanism of transplantation preservation is driven by propofol's action as a cytoprotective agent and membrane-targeted antioxidant. As such, propofol protects tubular cells from being affected by hypothermic injury *in vitro*, and the addition of its cyclodextrin complex to the preservation fluid during machine perfusion delivers it to the kidneys and prevents lipid peroxidation, while diminishing the early reperfusion period's renovascular resistance after transplantation [66]. However, recent clinical trials have suggested that volatile anesthetics, such as desflurane, used for anesthetic maintenance and preservation during transplantation are associated with better outcomes than intravenous anesthetics [67]. In fact, most currently available volatile anesthetics have been shown to efficiently preserve hepatic function and blood flow [68].

Furthermore, a recent study involving rats with obstructive jaundice evaluated the protective effects of various common intravenous anesthetics on renal tissues, and found that the incidence of postoperative AKI was higher in rats with obstructive jaundice than in those without it, and that obstructive jaundice causes renal tissue to become sensitive to anesthetic damage [69]. It was found that propofol and ketamine were the 2 anesthetic

agents that produced the least renal oxidative stress in this model of common bile duct ligation-induced obstructive jaundice [69]. Free radical injury in renal tissue during transplantation surgery was suggested to have significant importance in preventing related AKI.

Various clinical studies have helped elucidate the relationship between anesthesia and clinical AKI. A recent meta-analysis was conducted for remote ischemic preconditioning (RIPC) trials in patients prior to undergoing cardiac surgery. Although researchers found that there was a significant reduction in AKI when propofol was not used, no effects were observed in those who received both propofol and RIPC during surgery. This suggests that propofol may interact with the protective components of RIPC, thereby improving clinical outcomes [70]. Furthermore, another recent study compared the clinical outcomes of propofol and sevoflurane anesthesia on postoperative AKI [71]. A multivariable analysis of 4,320 colorectal surgery patients' medical records revealed that the incidence of AKI was significantly higher in patients who received sevoflurane than in those who received propofol, suggesting that anesthesia with propofol may be associated with improved clinical AKI outcomes for patients [71]. Additionally, another study consisting of a randomized placebo-controlled trial investigated whether dexmedetomidine prevents AKI following valvular heart surgery [72]. AKI incidence, morbidity, and ICU stay were all found to be significantly lower for patients who received dexmedetomidine than for those who received the placebo, suggesting that perioperative administration of dexmedetomidine may reduce the incidence and severity of AKI, thus improving clinical outcomes for patients undergoing cardiac surgery [72].

Regional Anesthesia

It has been found that the addition of bupivacaine to a depolarizing cardioplegia solution reduced cell damage and improved cardiac function after prolonged storage [73]. Bupivacaine's ability to decrease cell damage suggests that it may have some protective effects against renal IR injury.

In fact, several studies have found that epidural analgesia (EDA) reduces the incidence of acute renal failure. In a study that investigated the effect of EDA on renal blood flow in 13 healthy volunteers, researchers administered lidocaine 2% without epinephrine to establish a bilateral T6 epidural sensory block. They found that EDA did not significantly alter renal blood flow [74]. In fact,

EDA using lidocaine or bupivacaine is the preferred anesthesia method in renal transplantations because it displays lower toxicity for the recipient and renal allograft [75].

Furthermore, a review of trials with randomization of intraoperative neuraxial blockade showed that EDA reduces postoperative mortality and other complications, such as renal failure [76]. This finding is further reinforced by a meta-analysis, which found that EDA, in addition to general anesthesia, reduced the incidence of perioperative acute renal failure in cardiac surgery [77]. Lidocaine may provide protection against IR injury by preventing miRNA dysregulation. A recent study found that lung IR injury caused miRNA dysregulation, while lidocaine reduced these changes [78]. Further studies should be conducted to examine how lidocaine regulates miRNA expression.

In contrast, a recent study found that EDA may be a risk factor for postoperative AKI after major hepatectomy [79]. While attempting to elucidate the relationship between anesthesia and clinical AKI, it was found that for major hepatectomies, AKI incidence was significantly higher among patients who received EDA as compared to those who did not, suggesting that EDA may contribute to negative postoperative clinical AKI outcomes for patients [79]. However, since no significant difference in AKI incidence was revealed in patients undergoing minor hepatectomies, contradictory data suggest that EDA may have a beneficial impact during some types of surgery, but not others. Further studies are required to elucidate the clinical outcomes of EDA on renal function in different types of surgery.

Conclusion

Certain anesthetics seem to exhibit protective effects in patients through anti-inflammatory, anti-necrotic, and anti-apoptotic mechanisms. Additionally, intravenous anesthetics, such as propofol, are promising candidates for preventing or treating AKI, as well as IR injury. The effects of anesthetic drugs on renal function are particularly important in the context of kidney transplantation and preservation strategies. Although anesthetics may have important clinical implications, our understanding of the underlying mechanism of their renal protection is not fully understood. Further research is necessary to elucidate the molecular mechanisms of anesthetics, specifically those that contain lipids in their structure, to enable repurposing them for novel applications, such as transplant and organ-protective targets.

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Data Source

Research in both human and animals has contributed the data needed for this study.

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