Organoprotective effects of Dexmedetomidine: From bench to bedside

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Abstract

Dexmedetomidine (DEX) is a selective $\alpha_2$ adrenoceptor agonist. Unlike other agents using in anaesthesia, it has a unique ability to provide sedation as well as analgesia with a low predisposition to respiratory depression. DEX causing reduction in the sympathetic drive may lead to life-threatening hypotension and bradycardia; however, these side effects can make DEX perhaps more appropriate to be used for patients who require significant analgesia and at risk of tachycardia and hypertension. Except sedation and analgesic properties, DEX has profound organoprotective effects. Vast pre-clinical studies have demonstrated that DEX can protect against cerebral, cardiac, kidney, liver and gastrointestinal ischemia-reperfusion injury but clinical studies on these are extremely limited and warrant further studies including clinical trials.

Keywords: $\alpha_2$ adrenoceptor agonist; Dexmedetomidine; Organ injury; Organoprotection

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Introduction

Advances in technology and medicine has allowed us to manage organ injuries that were previously fatal, however even at the best of our abilities most organ damage is irreversible. Most common organ failure described are pulmonary, cardiovascular, renal, hepatic and central nervous system [1]. According to the World Health Organisation, ischaemic heart disease is the most common cause of death worldwide, closely followed by stroke [2]. Interruption to blood flow is the main cause of organ failure, which can occur in a variety of circumstances where there is a low blood pressure such as septic, cardiogenic and haemorrhagic shock.

Tissues become starved of nutrients and oxygen as well as accumulate toxic metabolites and carbon dioxide, leading to conditions such as ischaemic stroke and myocardial, mesenteric and nphric ischaemia. Organ failure is often associated with high morbidity and mortality; for example, around 50% of stroke survivors have significant morbidities due permanent neurological deficits [3], requiring prolonged hospitalization, long-term physiotherapy and care. This creates a significant burden to the individual, family as well as society; it has been estimated to cost £8.9 billion per year in the UK [4].

Multi-organ failure is the most common cause of death in intensive care [5], which can occur following different events such as injury and sepsis. The decline in organ function can occurs over a short period of time, which may provide a window of opportunity to intervene. There are many methods of preventative strategies available including, for example, therapeutic hypothermia [6,7], anaesthetic agents [8,9] and free radical scavengers [10]. However these are beyond the scope of this review, we will focus on the vital organoprotection afforded by $\alpha_2$ adrenoceptor agonist Dexmedetomidine. Herein we will discuss the literature available regarding the
organoprotection that DEX provides together with underlying mechanisms.

**Molecular mechanisms**

**Pharmacology and pharmacodynamics**

Dexmedetomidine (DEX) is a selective $\alpha$ 2 adrenoceptor agonist [11]; it has a $\alpha$2:$\alpha$1 selectivity ratio of 1600:1, as well as 8 times the specificity of $\alpha$ 2 receptors when compared with Clonidine [12]. Unlike other agents using for anaesthesia such as fentanyl [13], it has a unique ability to provide sedation as well as analgesia with a low predisposition to respiratory depression [11,14]. DEX is a sedative agent commonly used in Intensive Care Unit (ICU) in the United States and Australia [15,16]; unlike other drugs regularly used for sedation, it is neither a benzodiazepine nor an opioid. It is an active $\alpha$-isomer of medetomidine, a veterinary sedative and analgesic agent [17]. $\alpha$ 2 adrenoceptors are G protein coupled receptors (GPCR), stimulation results in activation of the pertussis toxin-sensitive guanine nucleotide regulatory protein [18,19], which inhibits the activity of adenyl cyclase [20], resulting in a reduction in cyclic adenosine monophosphate (cAMP); the subsequent effect on ion channels ultimately lead to decrease neuronal activation. DEX’s onset of action is 15 minutes and has a biphasic half life, initial half life is 6 minutes and the next half life is 2 hours [21]. Metabolism of DEX occurs hepatically by cytochrome P-450 (CYP-450), therefore may interact with other drugs and patients with liver dysfunction may require lower doses; majority of excretion occurs via the kidneys, however patients with renal dysfunction does not appear to require an adjusted dose [22].

**Sedative effect**

DEX acts the locus coeruleus to mediate its sedative effect [23,24], by stimulating central $\alpha$ 2 adrenoceptors to inhibit the release of noradrenaline. This allows for increase activity of inhibitory neurons such as $\gamma$-amino-butyric-acid (GABA) neurons [23,25]. High doses of DEX alone can induce significant anaesthesia in patients with complicated airways without inducing respiratory depression [26]. However, reductions to blood pressure and heart rate have been documented [27]. As mentioned previously, this may be considered as an advantage as it tend to normalize blood pressure and heart rate from elevated levels. Many studies have previously deemed DEX as unable to induce a good level of anaesthesia [28], however the doses they used were not as high as the doses used in the case study. Unlike other drugs, DEX lack neurotoxicity even at an extremely high dose [29]. Ma et al[16] concluded that DEX is a superior drug to propofol in providing conscious sedation and analgesia, providing a deeper sedation and higher patient satisfaction. Due to its safety profile and potential organoprotective effects, interest regarding its use in paediatric anaesthesia is rising[30].

**Analgesic effect**

DEX has been found to have analgesic properties in many animal models. The mechanism behind the analgesia lies within the spinal cord. It has been suggested that DEX acts on $\alpha$2A adrenoceptors in the spinal cord[31,32], modulating neurotransmission to reduce the activation of nociceptive pathways [33,34]. Some have also theorized that DEX accentuates and synergizes the actions of opioids [35]. Clinically, Jaakola et al [36] found DEX’s analgesic effects comparable to fentanyl. DEX has analgesic sparing effects; it has been shown to reduce the post-operative use of morphine [37-40] and alfentanil [41]. Therefore, when used in conjunction, side effects from high dose opioids such as drowsiness, constipation and histamine release can be significantly reduced. In addition, DEX also reduces the requirements of propofol [42,43] and midazolam [40]. Moreover, DEX was found to produce an additive effect, but not synergistic effect, when co-administered with nitrous oxide, a commonly used analgesic gas [44].

**Haemodynamic effect**

Surgical trauma activates stress responses, which leads to the release of endocrine factors such as vasopressin and cortisol [45], as a result blood pressure increases. DEX’s ability to stabilise haemodynamic parameters can be attributed to stimulation central $\alpha$ 2 receptors in the medullary vasomotor centre, resulting in a reduction in sympathetic outflow, increasing vagal activity as well as reducing noradrenaline release [14]; reducing heart rate, cardiac output and stroke volume, thus combating the intraoperative hypertension [46]. Acute pain can stimulate the sympathetic response leading to increase blood pressure, DEX can modulate pain by acting in the
spinal cord [11], therefore reducing the effect of pain-induced hypertension. A dose-dependent blood pressure decrease had been noted in healthy volunteers [14, 47].

Concerns have been raised regarding the use of DEX in ICU [21]. Although DEX does not induce respiratory depression, its haemodynamic effects may be unfavorable. Patients in ICU often have compromised circulations, for example, haemorrhagic, cardiogenic or septic shock. In addition, hypotension is a common side effect of epidural anaesthesia, which is commonly used in ICU to provide pain relief [47, 48]. Any further reduction in the sympathetic drive may lead to life-threatening hypotension and bradycardia. The haemodynamic effect of DEX is biphasic: initial bolus injection has been proposed to stimulate post synaptic α 2 adrenoceptors in vascular smooth muscle, leading to vasoconstrictive effects causing bradycardia and hypertension [49]. Subsequent continuous infusion, due to central sympathetic effects, leads to hypotension [43]. Severe bradycardia can occur, and progression to asystole but not death has been documented in one case study [49]. DEX is perhaps more appropriate for patients who require significant analgesia and at risk of tachycardia and hypertension [37], where patient vital observations can be closely monitored.

Organoprotective effects

The effects of DEX on organ injury, in particular ischaemic-reperfusion (I/R) injury, have been well documented. A unifying mechanism in which DEX operates is unlikely; as it appears that DEX have different effects depending on the cell type in which it is exposed to. Herein, we will examine the literature of the potential organoprotective effect of DEX.

Neuroprotective effects

Neurotoxic properties of anaesthetic agents have been thoroughly investigated [50-56]. Although avoidance is the best protective measure, certain surgeries cannot be prevented. This neurotoxic effect is of particular concern in the paediatric population, where general anaesthesia has been found to lead to neuroapoptosis in the developing brain and long term impairment [57, 58]. Anaesthetic agents in general, act by inhibiting synaptic neurotransmission, for example by potentiating γ-amino-butyric-acid type A (GABA_A), which in turn will inhibit stimulatory glutamate N-methyl-D-aspartate (NMDA) receptors. This silencing of neurotransmission at a critical period of synaptogenesis can lead to activation of neuronal apoptotic pathways and mediate neurodegeneration [59, 60].

**Acting via α2 adrenoceptor**

α2 adrenoceptor is thought to play in important role in the survival and growth signaling of developing neurons [61, 62], which involves activation of the Ras-Raf-pErk pathway [63]. Isoflurane is an inhalational anaesthetic associated with neurodegeneration, caspase-3 activation and long term neurocognitive deficits [53]. DEX has been found to attenuate isoflurane-induced neurotoxicity [64], the possible anti-apoptotic mechanism behind this is the activation of post-synaptic α2 receptors leading to the coupling of pERK-Bcl2 pathway via noradrenaline-mediate trophic system [65]. Many investigators used α2 adrenoceptor antagonists, such as yohimbine, to demonstrate the importance of the receptor in mediating the neuroprotective effect of DEX. In some cases, it was shown to completely obliterate the said effect [66-68]. However, in others the effect was only partially attenuated [65, 69]. This indicates the potential involvement of another receptor.

**Acting via I2 Imidazoline receptor**

Activation of Imidazoline receptors have been found to be neuroprotective [70, 71]. There are 3 subtypes of Imidazoline receptors; I₁, I₂ and I₃. The receptor associated with the neuroprotective effect is I₂, which had previously been associated with anti-nociception [72] as well as involved in monoamine breakdown [73]. Zhang et al found that DEX protects against oxygen glucose deprivation (OGD) in *in vitro*, predominately by activating I2 receptors and subsequently the PI3K/Akt pathway as well as upregulating hypoxia-inducible-factor-1α (HIF-1α), VEGF and RTP801 expression [69]. HIF-1 is an oxygen-dependent transcription factor that regulates many genes involved in survival [74]; VEGF stimulates angiogenesis and RTP801 protects against ischaemic damage [75].

**Involvement of Phosphatidylinositol 3-kinase (PI3K)/Akt and Extracellular-signal-regulated-kinase (ERK) 1/2 pathways**

PI3K/Akt and ERK1/2 pathways have been shown to mediate neuroprotection in multiple models of injury [76-81]. PI3K is an important transcriptional factor signaling pathway to mediate cell...
proliferation, growth and survival [82]. Phosphorylated PI3K activates Akt, which inhibits pro-apoptotic proteins such as BAD whilst stimulating pro-survival proteins such as Mdm2 [83], resulting in a net effect of cell survival. These 2 kinases have been found to partake in neuroprotection induced by various drugs [84,79,85]. ERK, also known as mitogen-activated protein kinase (MAPK), is an important protein kinase mediator of the MAPK pathway [86]. Specific to CNS, ERK pathway is vital for brain development and neuron proliferation [87]; it has been shown to play an important role in DEX-mediated neuroprotection [65,66]. Recently, Degos et al. found that astrocytic ERK activation facilitate DEX’s neuroprotective effects [67]. Zhu et al noted DEX upregulated Akt, ERK1/2 as well as glycogen synthase kinase 3β (GSK3 β ), these effects are inhibited by PI3K and MEK inhibitors demonstrating that both PI3K/Akt and ERK are involved in neuroprotection by DEX [88].

**Activating neurotrophic pathways**

Brain-derived neurotrophic factor (BDNF) is a neurotrophin important in neuronal survival and axon growth [89], an alternation in BDNF levels can lead to the activation of BDNF-dependent neuroapoptosis. Anaesthetic agents have been found affect BDNF levels differently in different parts of the brain [90], the effect is thought to correlate with the different expressions of neurotrophin receptors in the brain [57]. Anaesthesia-induced alteration of BDNF have been validated clinically by a human study that found a decrease in plasma levels following surgery [91], which positively correlate to cortical BDNF levels [92]. DEX has been shown to reverse the anaesthetic-induced serum BDNF reduction [93] as well as inducing BDNF in non-injury neuronal cultures [67].

Excitotoxic brain injury, also termed glutamate-induced brain injury, occurs in conditions such as stroke when there are excessive stimulation of excitatory receptors, leading to calcium influx into neurons activation of various enzymes which eventually lead to damage and cell death [94]. DEX has been shown to mitigate the neurodegenerative effects of excitotoxicity through α2 adrenoceptor activation [68], as well as reduce perinatal excitotoxic injury [95,96]. One of the mechanism in which DEX combats excitotoxicity is the induction of BDNF from astrocytes, which appears to acting via α2 adrenoceptors and subsequent phosphorylation of ERK1/2 [67].

**Synergistic effects**

Therapeutic hypothermia is often performed following I/R, it has been well validated in its ability to reduce apoptosis and neurodegeneration following cardiac arrest [97] and neonatal asphyxia [98]. DEX has been found to induce a dose dependent reduction on body temperature [99], which was mediated by α2A adrenoceptors [97]. This may contribute to the neuroprotective effect of DEX but it is unlikely to be the sole mechanism. Hypothermia have been found to increase pro-survival proteins such as Bcl-2 [99]; DEX has also been found induce anti-apoptotic protein expressions [66,100]. DEX has also been found to act synergistically with xenon, a well-validated neuroprotective anaesthetic gas [101]. When used in conjunction, lower doses of each agent were required to produce the same level of effect as when used as single agents; the cerebral infarct sizes were reduced and the protective neurological effect was long lasting [102]. Both interventions can reduce calcium influx mediated by hypoxia, which improves survival [103]. In addition, xenon also increases anti-apoptotic protein Bcl-2 expression[8]. Therefore when used together, these therapies may have synergistic effects; this calls for further research.

CNS hyperexcitation is responsible for producing the symptoms associated with severe alcohol withdrawal syndrome (AWS). Patients often require intensive care with multiple doses of benzodiazepines, intubation and mechanical ventilation. In a retrospective study, DEX was found to reduce benzodiazepine requirements, AWS severity score as well as the incidence of tachycardia and hypertension[104]. DEX has been suggested to be the primary agent to be considered in AWS due to its superior profile documented in several case studies[105,106].

In summary, DEX has been shown to prevent apoptotic cell death against a variety of injuries such as protein kinase inhibitor induced [107], isoflurane-induced [64], excitotoxicity [67], ischaemia [108], ischaemic-reperfusion injury [109] and OGD [69]. Current available literature suggests the stimulation of α2 adrenoceptors and 12 receptors, leading to the activation of ERK and Bcl2 neuroprotective signaling cascades [65,100].
Cardioprotective effects

In various animal models, DEX has been found to be cardioprotective against ischaemia [110-112]. Regarding human studies, DEX has also been found to reduce plasma levels of cardiac troponin I and myocardial creatine kinase following coronary artery bypass graft surgery [113]; it was also found to improved cardiac outcomes in non-cardiac surgeries [114], however it is worth noting that incidence of perioperative hypotension and bradycardia was raised in the DEX groups.

The mechanism of cardioprotection can be divided into two; directly acting on the cardiomyocytes and indirectly by acting on the central nervous system. DEX has central sympatholytic effects that may be counteract ischaemic changes by affecting haemodynamic parameters, notably by reducing the heart rate and contractility thereby reducing the oxygen demand of the myocytes [115]. It has been suggested that catecholamines such as noradrenaline can worsen myocardial injury [116]; DEX can reduce catecholamine levels by acting on pre-synaptic receptors leading to decrease in neurotransmitter release, it has been documented to reduce plasma noradrenaline levels [117,118]by acting centrally to induce sympatholytic effects, thereby attenuating any further damage to the myocardium.

On the other hand, the evidence for direct action of DEX on cardiomyocytes is mounting. Ibaceche et al [110]identified α 2 adrenoceptors in cardiomyocytes and found that the cardioprotective effects of DEX was mediated by α 2 receptor stimulation and subsequent activation of PI3K/Akt signaling. As mentioned previously, activation of Akt and ERK1/2 is neuroprotective, but they had been shown to be cardioprotective [119-121]. Interestingly, the activation of endothelial nitric oxide synthase (eNOS) was noted, which supports the theory of cardioprotection by coronary artery vasodilation increasing the blood supply. In stark contrast, Okada et al [111]concluded DEX pretreatment reduced coronary flow thereby have its protective effects by preconditioning cardiomyocytes, leading to a reduce in infarction size when followed by I/R. Despite the similar experimental protocol, these 2 studies had conflicting finding; this warrants further investigations. It is potentially worth mentioning that although Ibaceche et al did not measure coronary flow, no ischaemia was found DEX pretreatment; additionally, the authors utilized an in vivo model as well as an ex vivo model, which may more representative. In a pig model, DEX reduced the incidence of reperfusion induced ventricular arrhythmias as well as improving recovery by acting directly on cardiomyocytes [118].

Hepatoprotective effects

Mechanisms of hepatic injury

Hepatic I/R injury is a consequence of liver transplantation and is the main cause of graft dysfunction [122]; it can also occur following surgery, trauma, heart failure and shock-resuscitation. It is a complex event involving many cellular and molecular changes, the series of events can be divided into oxygen-dependent and oxygen-independent [123]. Oxygen-dependent events result in the production of reactive oxygen species, which can directly damage cells leading to apoptosis; Oxygen-independent events include pH changes, inflammatory response recruiting cytokines and chemokines.

Anti-inflammatory effect of DEX

It has been proposed that DEX may have a role in sedation and modulation of liver dysfunction in septic patients in ICU, as it was found to reduce liver injury associated with sepsis [124]. In addition, Venn et al [41] had described the potential of DEX induced attenuation of surgical inflammatory response, specifically IL-6. In a murine model, DEX had been shown to successfully reduced liver damage assessed by histopathological parameters such as sinusoidal congestion, necrosis and loss of glycogen deposition [125]. DEX diminished the increase of malondialdehyde (MDA) induced I/R injury [126], an important indicator of oxidative injury [127]as it is produced by lipid peroxidation, as well as increased the activity of anti-oxidants such as catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) and glutathione peroxidase (GPx) [125]. Several other animal models have also identified this inhibitory effect of DEX on I/R injury induced MDA increase [117,128]. Although the exact mechanism is unknown, some have speculated that DEX has its hepatic protective effect by activating pre-synaptic α 2 receptors, inhibiting the release of catecholamine [117,129]. Catecholamine catabolism leads to free radical production, which in turn can induce lipid peroxidation and eventually cell injury [130]; hence
reducing catecholamines have the potential to reduce liver injury.

**DEX as an anti-oxidant**

To investigate the damage of IR injury, oxidant and anti-oxidant markers had been used as the early injury process is mediated by ROS [131]. DEX can reduce hepatic I/R injury by promoting anti-oxidant activity, leading to a reduction of oxidant markers and an increase of anti-oxidant markers [132]. Many anti-oxidants have been found to reduce hepatic I/R injury in animal models, however due to the extensive side effect profiles they cannot be translated to human studies. DEX has the added benefit of being available at the time of injury when used as an anaesthetic agent. DEX have been found to have anti-oxidant effect in the brain [133], gastrointestinal tract [134] and testicles [135,128]. This effect is mediated by the increase of antioxidant enzymes such as catalase and superoxide dismutase, reduction in lipid peroxidation and tissue nitric oxide production. However, the exact molecular mechanism responsible remains undetermined.

**Renoprotective effects**

**Mechanisms of renal injury**

Renal injury occurs following hypoperfusion due to a multitude of causes, such as septic and cardiogenic shock or following major surgeries. This is often followed by a period of reperfusion after the blood supply is re-established; damage is most strife in this period of time [136]. The subsequent reperfusion leads to the formation of reactive oxygen species (ROS), which damage cellular structures, the proximal tubular cell polarity is lost as a result. Adhesion molecules begin to infiltrate and impair peritubular and cell-matrix adhesion structures [137]. At the same time, inflammatory cytokines cascade are activated as a result of an acute inflammatory response, further stimulating the expression of adhesion molecules and cellular infiltration; this leads to a vast amount of cell death [138]. DEX has bradycardic and hypotensive effects, therefore logically it should worsen hypoperfusion. However DEX has been found to inhibit vasopressin release, thereby enhancing renal blood flow and glomerular filtration, subsequently increasing urine output [139,140]; this can reduce the extent of hypoperfusion and thus attenuate injury. α 2-adrenoceptors have been found in the renal tubules as well as vasculature [141,142], therefore DEX can have direct effects on the kidneys.

**Anti-inflammatory effect**

Many studies have established the anti-inflammatory effect of DEX on renal injury, such as reduction of TNF-α, IL-6, ICAM-1 and iNOS expression [143-146]. α2 adrenoceptor agonists have been found to influence cytokines release [147,148]. DEX acts via α 2-adrenoceptors to reduce proinflammatory cytokine expression such as in a sepsis-induced acute kidney injury model; in the same model it was shown to increase expression of bone morphogenetic protein-7 (BMP-7) [144]. BMP-7 suppresses the expression of TNF-α in proximal tubule epithelial cells [149], it has been found to regulate response to kidney insult and improve survival [150]. TNF-α is a powerful chemoattractant for neutrophils and aids neutrophil migration [151], which has been shown to mediate I/R damage [152]; whilst TNF-α binding proteins can reduce renal I/R injury [151]. IL-6 is a pleotropic cytokines, meaning it has both pro-inflammatory and anti-inflammatory properties; it has been shown to increase following renal injury [144-146], in animal models it can exacerbate renal failure. IL-6 increases the expression of adhesion molecules such as ICAM-1 and E-selectin, allowing the recruitment and infiltration of more leukocytes into the kidneys and mediate damage. IL-6 production by macrophages is one of the first events in reperfusion injury, which is mediated by toll-like receptor 4 (TLR-4) activation. High-mobility group protein B1 (HMGB-1) is released by dying cells and stimulates TLR-4 to initiate proinflammatory NFkB cascade. DEX inhibits TLR-4 and HMGB-1 [153,141], thus reduces macrophage IL-6 production. This anti-inflammation effect of DEX was also found in models of endotoxaemia [154]. Other than the renal damage, renal I/R can lead to remote organ injury as the cytokines and chemokines enter the blood stream and travel to distant organs, such as the lungs. By reducing the inflammatory response, DEX was able to reduce remote lung injury[143].

**Janus kinase/signaling transducer and activator of transcription (JAK/STAT) signaling cascade**

Si et al [145] have found the potential molecular mechanism behind DEX’s renoprotection against renal I/R injury. JAK/STAT signaling cascade can modulate gene expression by responding to various cytokines and growth factors [155]. This pathway
has been shown previously to be involved with acute renal injury induced by ischaemia [156], as ischaemia produces a mass amount of proinflammatory cytokines such as interferon γ (INF-γ), interleukin-1 (IL-1) and tumour necrosis factor α (TNF-α) [157]; which can activate JAK/STAT pathway. As mentioned previously, DEX can reduce cytokine release, as a result JAK/STAT pathway activation is diminished. In addition, DEX has also been shown to reduce the expression and phosphorylation of proteins involved in the pathway such as JAK, STAT1 and STAT2. DEX can reduce intercellular adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1) and caspase-3 expression suggesting it stops the progression of injury by reducing cellular infiltration such as granulocytes and macrophages [145] as well as halts cell death. These findings suggest that DEX’s renoprotection is multi-pronged.

**PI3K/Akt pathway**

Akt activation has been found to protect against injury induced by I/R in the kidney [158]. PI3K/Akt has been implicated as a mechanism of neuroprotection, however the molecular effect may also apply in other organs such as the kidneys; it promotes cell survival by inhibiting the intrinsic apoptotic pathway [159]. In the kidneys, DEX has been found to reduce the expression of caspase-3 following I/R injury [145]; another study found that it increased Bcl-2 and Bcl-xL in the brain [100]. DEX protects against increase in creatinine and renal failure induced by I/R injury by activation of Akt in α2-adrenoceptor dependent and independent pathways [141].

**Contrast-Induced Nephropathy (CIN)**

Contrast-enhanced imaging allows for better visualization of internal structures and is commonly performed. Contrast-induced nephropathy (CIN) is defined as an increase of 0.5mg per deciliter of serum creatinine level, or a 25% increase from baseline, following exposure to contrast medium [134]. It is the third most common cause of inpatient acute renal failure [160], although it only occurs in 1-5% of the general population, in certain patient demographics it can be up to 50% [161]; just under 1% of patients require dialysis [135]. CIN increases length of hospital stay, which in turn can increase the risk of nosocomial infection and cardiac events [155]. Some of the risk factors for contrast-induced nephropathy are age >75, systolic pressure of <80mmHg for more than 1 hr in duration, diabetes, heart failure etc [116]. There is currently a lack of CIN prophylaxis because of the poor understanding in the pathogenesis; most of studies look at hydration [157,144] and vasodilation [149,150,158] to improve renal perfusion, but none show convincing results. Use of anti-oxidants [150,158] do not reduce incidence and extracorporeal removal of contrast techniques such as haemodialysis can even be detrimental [162,163]. α2 adrenergic agonists have been found to attenuate CIN in mice [164]; DEX treated animals have significantly reduced serum creatinine and injurious markers. The mechanism may be the increase of outer medullary perfusion as DEX act on α2 adrenoceptors to reduce sympathetic tone, thus reducing vasoconstriction to increase renal blood flow [146].

In summary, DEX has been shown to protect against a variety of renal injury via multiple mechanisms. DEX may be advantageous to patients undergoing surgery with existing renal issues such as low eGFR.

**Gastrointestinal protective effects**

Intestinal I/R injury can occur in any situation where the circulation to the gut becomes compromised for a period of time and then returns back to normal, such as severe septic shock, major surgery and small intestine transplantation. Acute mesenteric ischaemia is also one of the causes; it is a medical and surgical emergency [165], requiring prompt intervention. Treatment involves re-establishing the blood supply to the ischaemic bowel, which can lead to I/R injury leading to ROS and inflammatory factor release in the gut [166]. Mortality is high even with rapid diagnosis and treatment [167], and it is often complicated with multi organ failure. Anaesthetic agents have been investigated for their gastrointestinal protective effect [168-170], as they will be readily available if they were used during surgery. This also applies to DEX, however the literature available regarding GI protection in particular is relatively limited.

DEX mitigates intestinal and renal injury following mesenteric I/R according to histological appearances [171]. Zhang et al [172] showed that DEX can reduce intestinal mucosal epithelial apoptosis following intestinal I/R injury; this effect was only observed when DEX was used before injury, not after. This suggests that timing of DEX administration may have a role in its protective...
effect; if DEX was the anaesthetic agent of choice, it will be administered before the injury therefore will be able to provide its organoprotective effect. The oxidative stress marker MDA was significantly reduced with DEX pretreatment, whilst enzymatic anti-oxidant such as CAT and SOD increased in activity [171]. This effect has also been found in murine testicular model [173,128], liver model [126]and in humans during tourniquet injury [174]. Although recently Bostankolu et al [175] were unable to replicate the protective effect of DEX following tourniquet injury, this warrants for further investigations.

Clinical evidence of organoprotection of Dexmedetomidine

Studies have shown that benzodiazepines, recommended drug for sedation in ICU, increases the risk of delirium [176]. The mechanism of benzodiazepine induced delirium has been postulated to be due to the activation of GABA_α receptors, which can affect other neurotransmissions in the brain leading to an altered mental state [177]. Delirium is a strong predictor of increased length of hospitalization, 6 month mortality and cost of care [178,179]. DEX can reduce the rate of delirium in ICU [170,181]; the MENDS double-blind, randomize controlled trial found that DEX sedation in patients requiring mechanical ventilation produced less coma and more days alive without delirium when compared to lorazepam, which is the current recommended sedative in ICU [182]. This suggests that DEX does not lead to a neurotransmitter imbalance as severely as benzodiazepines, as it acts via α2-adrenoceptors rather than GABA_α receptor.

Future prospective

The most common side effect of DEX noted is bradycardia. Although a slight bradycardic effect this may be of advantage as mentioned previously, life-threatening cases have been documented [99,49]. These haemodynamic effects are due to the peripheral activation of α2 adrenoceptors by DEX, therefore there is a potential that a drug more selective to central α2 adrenoceptors may reduce these side effects and should be investigated.

Currently, there are many trials that authenticate the safety of DEX as a sedative used in ICU. Many of them compare DEX with other sedative agents that are currently used such as lorazepam and midazolam. However, these trials each have their own advantages and shortcomings. The MENDS trial [182] although small, has the advantage of long-term data looking at 12-month time to death. Riker et al [183] did not look at follow-up, but had a larger sample size as well as larger demographic of patients with 5 countries involved. Larger clinical trials are warranted in the future to support for a more widespread use of DEX.

Competing interests

There is no conflict of interest.

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