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Briefing on the use of ketamine for management of COVID-19

Direct evidence for Ketamine in COVID-19

There is no direct evidence for Ketamine as a therapy for COVID, though this has been suggested as a consideration on social media

- No published paper or case report was found in MEDLINE, LitCovid, Cochrane Reviews, Google Scholar, WHO dealing with the use of ketamine as a therapy for COVID-19
- Individuals have taken to social media to raise concerns that Ketamine increases respiratory secretions, but is considered generally safe to use, especially for intubation

Interaction between ketamine and inflammatory cytokines

There is mixed evidence on the effect of ketamine on IL-6 and other inflammatory cytokines.

There is both *in vitro* and *in vivo* evidence that ketamine can result in immunosuppression and reduced inflammatory cytokine production. Reviews of the topic indicate that *in vitro* studies have shown that there is ketamine-induced inhibition of transcription of several cytokines, including IL-6, a target of many drugs under investigation for the treatment of COVID-19.

There have been several randomized controlled trials investigating the effect of Ketamine on IL-6 levels. Most of the literature comes from the peri-operative world.

- There is a meta-analysis of 6 studies that shows anti-inflammatory effect in all studies included in the meta-analysis. (*Dale et al.)*
    - There was no dose response.
- There are several positive studies in the published literature associating Ketamine with lower serum levels of IL-6
    - All studies are from the perioperative world
    - Doses ranged from 0.15mg/kg to 3mg/kg bolus doses
        - Multiple positive studies investigated the use of induction dose ketamine followed by an infusion of ketamine.
        - There was no direct comparison between different doses in any study
- Multiple other RCTs have found negative results, with no lowering of IL-6 or other inflammatory cytokines or pro-inflammatory markers.
    - Doses ranged from 0.25mg/kg to 1-2mg/kg bolus
        - One study protocol investigated 1-2mg/kg bolus followed by an infusion of 50mcg/kg/minute (paediatric literature)

Background information

Title: Mechanisms of ketamine-induced immunosuppression

First author: Liu, F.L.

Published in: Acta Anaesthesiologica Taiwanica 2012

Link: https://www.sciencedirect.com/science/article/pii/S1875459712000951

Research question: Review the literature on the immunomodulatory effects of ketamine and possible signal-transducing mechanisms

Type of study: Review Paper

Key points: Studies with in vitro data support the theory that ketamine exerts suppressive effects on macrophage functions via inhibition of phagocytic activities, oxidative ability, and TNF-a, IL-1b, and IL-6 mRNA synthesis; ketamine-induced suppression of TNF-a and IL-6 synthesis occurs at the transcriptional level.

Table 1
Effects of ketamine on immunosuppression.

Study targets	Importance	Ketamine effect
NK cell count and activity	Kill viral-infected or tumor cells	Reduced[10,11]
CD11b, CD16, CD18, CD62L	Cell adhesion and migration, bacterial phagocytosis	Reduced[12–14]
IL-1β, IL-6, TNF-α	Proinflammatory cytokines	Reduced[15–25]
IL-2	Cellular and humoral immune response	Preserved[26,27]
Mitochondrial membrane potential	Macrophage function	Reduced[16]
LPS/LBP binding	Activate inflammation response	Reduced[17]
Ras/Raf/MEK/ERK/IKK	Signal pathway for proinflammatory cytokines	Inhibited[7,17,18,28,29]
NFκB, AP-1	Transcription factors for proinflammatory cytokines	Inhibited[7,14,20–22,29–31]

Superscripts indicate reference numbers.
AP = activator protein; ERK = extracellular signal-regulated kinase; IKK = inhibitor of kappa B kinase; IL = interleukin; NF-κB = nuclear factor-kappa B; TNF = tumor necrosis factor.

The anti-inflammatory effects of ketamine: state of the art
S. Loix et al. Acta Anesthe Belg., 2011
https://www.ncbi.nlm.nih.gov/pubmed/21612145
Objective: Literature review providing complete overview on the immunomodulatory properties of Ketamine
Type of Study: Lit Review

Key Points:

- Ketamine alters **innate** immune system
  - **Macrophages:** inhibits cytokine production (IL-6 and TNFa) and NO in macrophages.
    - Alters bactericidal activity
  - **Neutrophils:** reduce free radical, cytokines, phagocytosis, diapedesis (animal/human models).
  - **Platelet:** inhibits platelet aggregation and activation (no influence on coagulation), rather diapedesis.
- Ketamine alters **pro-inflammatory** cytokines
  - Reduction in **TNFa** production LPS stimulated mice (1994).
    - Confirmed in healthy volunteers
  - Reduction in in **IL-6** seen across many clinical studies.
  - Ketamine shown to have **strict** inhibitory effect on pro-inflammatory cytokines when compared to thiopentone, etomidate, midazolam, and fentanyl.
    - No change was seen in the absence of immunostimulation (LPS, gram + enterotoxin).
    - Minimal, but present, post-stimulation anti pro-inflammatory response.
      - Interaction with NFkB
  - Documented reduction in IL-6 post liver transplantation with ketamine administration.

Bottom Line

- Ketamine has animal/human in vitro and in vivo evidence (of varying quality) suggesting a correlation with alterations in innate immune system and pro-inflammatory cascade (IL-6 production) when given predominantly **before** an immunostimulating insult, which are **not apparent** in other forms of anesthetics to date (2011).
- Further investigation as to its active role when inflammation has already been initiated.

Studies demonstrating statistically significant effects on IL-6

Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis.
Dale, Ola et al. Pain Medicine, 2012
https://www.ncbi.nlm.nih.gov/pubmed/22826531
Objective: Examine the effect of perioperative Ketamine administration of post-op inflammation (IL-6 biomarker).
Type of study: Systematic Review/Meta Analysis (PRISMA)

Key methodological points (SR)

- PubMed, Scopus, Embase, Web of Science, and CENTRAL (13/10/11)

- **Inclusion**: English clinical RCTs, ketamine intervention, outcomes had to relate to inflammation/immune modulation
    - If primary outcome was not clinical, **surrogate outcomes** had to be measured **in vivo** or manipulation of sample **ex vivo.**
- Reviewed and rated by two assessors independently.
- **Internal validity** assessed using National Health Service Centre for Reviews and Dissemination guidance.
    - Data analysed in accordance with GRADEs approach (evidence profile for the outcome)
    - Process reported through PRISMA requirements (**review protocol was not registered** as recommended)

Key methodological points (MA)

- Inclusion: Plasma [IL-6] within **first 6 post-op hours** (6hr time cut off chosen for very specific reasons, refer to paper).
    - Extracted from each RCT within each study.
    - Differences between groups pooled using random effects meta-analysis model and I2, X2, and funnel plot were generated.

Results (Meta-analysis)

- **Primary outcome:** Postoperative plasma/serum IL-6 levels after perioperative ketamine infusion
- Anti-inflammatory effect demonstrated **in all 6 studies** included in the meta-analysis
    - **Mean difference -71** (95% CI, -101 to -41) pg/mL (p <0.001).
        - No dose response
    - **Mean difference - 50** (95% CI, -75 to -25) pg/mL, when including studies with additional potent antiinflammatory drugs given.
    - **I2 = 91.1%** across all studies (**highly heterogenous**)
        - I2= 0.0% in cardiopulm bypass studies
- Other notable findings:
    - **No publication bias** (Egger's funnel plot)

Results (Systematic-Review)

- **14 studies** were included, n=684, 12 studies comparing 2 groups, 12 studies in adults.
    - 10 double-blinded, 2 single-blind, 2 open
    - CPB=7, Cardiac surgery off-pump=1, major abdo operation=4, thoracic=1, cataract=1
    - 13/14 underwent GA, a varying number received epidural in control/intervention group.
    - **2 high quality, 9 medium quality, 3 low quality** (excluded from qualitative analysis)**.**
    - **5 studies** concluded that racemic or (S)-ketamine significantly reduced inflammatory response post-op, as seen by the primary outcome.
- **Primary outcomes:** 12/14 surrogate (blood markers of inflammation), 2/14 ex vio ("stimulated" blood samples), 1/14 neurodevelopment,
    - **13/14 measured IL-6**
    - Samples drawn post-operatively **(4hrs-8days)**
    - **High evidence profile** (GRADE) for evidence in evaluation for intraoperative ketamine administration on post-op IL-6.
- **Intervention (dosages)**

    - 12/14 used racemic ketamine, 13/14 **given at induction** of GA.
        - (S)-ketamine single dose (2-4mg/kg) followed by infusion (1.5-3.5mg/kg/h),
        - Racemic ketamine single dose (1-2mg/kg) followed by infusion (1.5-3.5mg/kg/h)
        - Low dose (S+)-ketamine infusion (0.075mg/kg/h)
        - Racemic ketamine infusion 1mg/kg over duration of surgery
        - Low single dose (0.15-0.5mg/kg)
- Other Notable outcomes:
    - CRP, IL-8, TNF-a did not demonstrate consistent results.
    - 5 chinese papers, 2 excluded ⅓ **did show effect** similar to the meta-analysis (IL-6).
    - Interesting consistent **IL-10 increase** seen **across majority** of papers.

Major caveats
(Confounding factors, bias, limited generalizability, etc)

- **3/11** studies administered (methylpred, dex, ibuprofen) as premedication or during operation, they were removed from the quantitative analysis.
- **Effect size was variable** across studies (e.g. surgery type)
- Data was inconsistent regarding **duration of action** of intraoperative ketamine (e.g. 6hr-8days).
- IL-6 is a "narrow" or indirect measure of inflammation and its clinical consequences.
    - **No dose response** was seen, limiting the evidence for the relationship.
    - **No clinical outcome was documented.**

Bottom line

- Intraoperative ketamine **has an anti-inflammatory effect**, as indicated by the meta-analysis showing a considerable reduction in circulating concentrations of the proinflammatory cytokine IL-6 during the **first 6 hours after surgery,** although highly heterogenous.
    - Majority used racemic ketamine single dose (1-2mg/kg) followed by infusion (1.5-3.5mg/kg/h)
- **Large, high evidence profile, effect size** was demonstrated, even when including studies using potent anti-inflammatory drugs (methylprednisolone, dexamethasone, ibuprofen).
- We are limited in our ability to correlate these findings to clinical outcomes. Clinical outcome studies are still warranted to provide further evidence on ketamine dosage, duration, and clinical correlation.
    - The evidence presented in this review suggests that **subanesthetic single doses** should be examined first, to explore clinical correlation

- We are further limited by the generalizability of these findings, given that ketamine was often administered prior to the immunostimulatory event (often surgery), when people with COVID-19 will most likely be in active inflammation.

Title: Preoperative low dose ketamine reduces serum interleukin-6 response after abdominal hysterectomy.

First author: Roytblat, L.

Published in: Pain Clinic 1996

Link:
https://www.researchgate.net/publication/288789337_Preoperative_low_dose_ketamine_reduces_serum_interleukin-6_response_after_abdominal_hysterectomy

Research question: Does preoperative ketamine effect IL-6 production?

Type of study: RCT

Key methodological points:

- 22 women (<60yrs), ASA grades I & II, undergoing elective abdominal hysterectomy.
- Randomized into two equal size groups, one received 0.15mg/kg ketamine and the other equal amount of saline (control group).
- Serum [IL-6] measured pre-op, peri-op, as well as 4, 24, 48, & 72h post-op.

Results:

- Mean age of around 50 in both groups.
- Serum [IL-6] low <5pg/ml in both groups pre- & peri-op.
- Serum [IL-6] significantly lower in Ketamine group at 4hr ($p<0.0005$), 24 and 48hr ($p<0.05$).
- Serum [IL-6] returned to baseline at 72hr in both groups.
- Control group also had significantly higher BP and HR.

Major caveats: Small sample size, single-gender, no elderly patients, operative setting only (not critical illness)

Bottom line: Subanesthetic doses of ketamine given during the induction of anesthesia **reduced serum IL-6 levels** in women undergoing hysterectomy.

The effect of a small dose of ketamine on postoperative analgesia and cytokine changes after laparoscopic cholecystectomy.
Kartalov A et al. Prilozi, 2012
https://www.ncbi.nlm.nih.gov/pubmed/22983102
Objective: Effect of small-dose ketamine on TNFa, IL-1B, and IL-6 and post=op pain in patient undergoing lap-chole
Type of Study: RCT

Key methodological points

- Inclusion: Patients ASA I or II. Elective Lap Chole
- Exclusion: Severe hepatic, renal, CV, psych, malignancy, immune system, AUD, inability to understand protocol.
- Exposure/intervention:
    - Premedicated diazepam 5-10mg PO 90min prior
    - On arrival: midazolam 2-3mg
    - GA induced: fentanyl 2–3 μg/kg , propofol 1–2 mg/kg , atracurium 0.5 mg/kg, and maintained with NO mixtures with O2 and Sevo.
    - **Group A (ketamine): Racemic 0.25 mg/kg-1 ketamine.**
    - **Group B (control):** NaCl 0.9%
    - **Analgesia post-op (all patients):** 100mg ketoprofen IV +/- 100mg tramadol IV (depending on pain control)
- Surrogate vs clinically relevant: All surrogate

Results

- Group A; n=25, Group B; n=25
    - All matched case controls.
- Primary outcome: serum [IL-6] postoperatively
    - **Group A mean IL-6** values were **significantly lower** than **mean** values in the **Group B**, at **4 hours** (Studentt-test; p = 0.0099), **18 hours** (Student t-test; p = 0.0013) and **24 hours** post-operation (Studentt-test; p = 0.0086).

Major caveats
(Confounding factors, bias, limited generalizability, etc)

- **All** received **postoperative potent anti-inflammatory drugs.**
- **No indication** of methods for randomization, blinding, allocation concealment etc.

Bottom line
Low-medium grade evidence of correlation between attenuation of proinflammatory cytokine IL-6 with small dose ketamine (0.25 mg/kg-1 ketamine) administration in patients undergoing elective lap chole.

Ketamine Attenuates the interleukin-6 response after cardiopulmonary bypass
Leonid, R, et al.
Anesthesia & Analgesia, 1998
https://journals.lww.com/anesthesia-analgesia/Fulltext/1998/08000/Ketamine_Attenuates_the_Interleukin_6_Response.6.aspx
OBJECTIVE: Compared effects of adding small-dose ketamine to opioids during general anesthesia on IL-6 levels in patients undergoing cardiopulmonary bypass (CPB) via coronary artery bypass grafting (CABG)
Randomized, double-blinded, prospective trial

Methodology:

- POPULATION: Patients undergoing elective CABG (n=28) with standardized anesthetic regimen of large-dose fentanyl
- EXCLUSIONS: LVEF <40%, those requiring pre-operative inotropic or intra-aortic balloon pump support, uncontrolled systemic diseases (i.e. diabetes, hypertension, or renal failure), postoperative low cardiac output syndrome, those requiring administration of NE

- INTERVENTION: Patients were randomized to one of 2 groups - a control group that did not receive ketamine, but received an equal amount of isotonic sodium chloride solution and a ketamine group that received a bolus of small-dose ketamine (0.25 mg/kg) during induction of anesthesia
    - Pre-medicated with IM morphine 0.1mg/kg and IM scopolamine 0.3-0.4mg in addition to their usual cardiac medications 60 mins prior to induction
    - Received 1-2 mg IV midazolam and oxygen on arriving to OR
    - General anesthesia consisted of IV fentanyl 15ug/kg, midazolam 10mg and pancuronium 0.1mg/kg
    - Maintenance of anesthesia was provided via bolus of fentanyl (3-5ug/kg) and midazolam (1-2mg)
- OUTCOME: Blood samples were drawn pre-operatively, post-operatively 0 h, 4h, 24h, 48h and post-op days 3-8 for serum IL-6 levels

Results:

- PRIMARY OUTCOME: serum IL-6 levels pre-op, post-op 0h, 4h, 24h, 48h, 3-8 days
    - No significant difference in characteristics or baseline IL-6 (pre-op) between groups
    - In both groups, pre-op levels of IL-6 were low and did not differ significantly (9 +/- 1 pg/mL in control group vs 6 +/- 9 pg/mL in ketamine group)
    - Post-op 0h and 4h, serum IL-6 levels increased in both groups, but increase in the ketamine group was significantly less than that in the control group [(200 +/- 44 pg/mL in control group vs 70 +/- 38 pg/mL in ketamine group; $P < 0.05$), (239 +/- 48 pg/mL in control group vs 149 +/- 74 pg/mL in ketamine group; $P < 0.05$) respectively]
    - Serum IL-6 levels in both groups began to decrease 24h post-op
        - Significant differences in IL-6 levels between the two groups at 24 h, 48 h, and on Postoperative Days 3-6 ($P < 0.05$)
        - On post-op day 7, serum IL-6 level was still higher than the pre-op levels in both groups, however level in ketamine group was still significantly lower than that in control group (44 +/- 10 pg/mL in control group vs 21 +/- 2 pg/mL in ketamine group; $P < 0.05$)
    - Serum IL-6 levels in both groups were about the same by post-op day 8
- OTHER NOTABLE FINDINGS
    - No mortality in either group

Major Caveats:

- Small sample size RCT - only $n < 20$ patients each in control and ketamine groups

Bottom Line:

Small dose of ketamine added to opioid-based anesthesia, suppresses increase of serum IL-6 **postoperatively** after cardiac surgery

Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass
Welters, ID
BJA
https://bjanaesthesia.org/article/S0007-0912(17)33318-4/pdf

- In patients undergoing elective on-pump CABG, (S)-(+) ketamine at doses of **1-3mg/kg then 2-4mg/kg/hr** as the sole analgesic reduced IL-6 & IL-8 and increased the pro-inflammatory IL-10 6hrs post aortic unclamping

Effect of Ketamine on Inflammatory and Immune Responses After Short Duration Surgery in Obese Patients
Roussabrove, E
The Open Anesthesiology Journal
https://benthamopen.com/ABSTRACT/TOATJ-2-40

- In adult patients with obesity undergoing short elective surgery, **ketamine 0.15mg/kg** pre-op attenuates immediate increase in IL-6 at 4hrswith a trend towards possible sustained effect

Low-dose ketamine affects immune responses in humans during the early postoperative period
Beilin et al.
British Journal of Anesthesia
https://bjanaesthesia.org/article/S0007-0912(17)35469-7/fulltext

- In adults undergoing elective abdominal surgery, **ketamine 0.15mg/kg** induced attenuation of IL-6 and TNF-a production.

Effects of Ketamine on Serum and Tracheobronchial Aspirate Interleukin-6 Levels in Infants Undergoing Cardiac Surgery
Zeyneloglu et al., 2005
J Cardiothoracic Vasc Anesth
https://www.ncbi.nlm.nih.gov/pubmed/16130059

- In infants 2-24mo with congenital heart defects who received perioperative steroids, ketamine 1-2mg/kg induction and 25-75mcg/kg/min infusions did not have decreased serum & tracheobronchial aspirate IL-6 compared to thiopental induction & isoflurane maintenance

Effect of single compared to repeated doses of intravenous S(+) ketamine on the release of pro-inflammatory cytokines in patients undergoing radical prostatectomy
Mohammed Ali, H & Mokhtar AM.
Anesthesia Essays and Researches, 2017
http://www.aeronline.org/article.asp?issn=0259-1162;year=2017;volume=11;issue=2;spage=282;epage=286;aulast=Ali
OBJECTIVE: evaluate effect of pre-incision single or multiple doses of ketamine on pro-inflammatory cytokines (i.e. TNFa and IL-6)
Prospective randomized, controlled, double-blinded trial

Methodology:

- POPULATION: Male patients >45 years old (n=60) scheduled for radical prostatectomy under combined epidural-general anesthesia

    - EXCLUSIONS: Physical Status ASA classes III or more, BMI > 35, preexisting neurological or psychiatric disorders, chronic drug abuse, use of drugs affect immunity (e.g. chemo, hormonal therapy), uncontrolled diabetes, renal, hepatic, hypertensive patients, contraindicated for epidural catheter insertion and hypersensitivity for anesthetics/drugs used
- INTERVENTION: Patients were randomly divided into 3 groups (20 in each group). Group 1 received combined anesthesia without ketamine (control), Group 2 received combined anesthesia and ketamine (IV 0.5mg/kg) as a **single** pre-incision dose, Group 3 received combined anesthesia and ketamine as pre-incision (IV 0.5mg/kg) and repeated doses of ketamine (0.2mg/kg) in 20 min intervals up to 4 hours into surgery
    - General anesthesia consisted of propofol (2 mg/kg), fentanyl (1 μg/kg), and atracurium (0.5 mg/kg)
    - Maintenance of anesthesia used an infusion of atracurium at rate of 8 μg/kg/min and 1%–1.5% isoflurane
    - 5 ml of levobupivacaine 0.25% was administrated in the epidural catheter
- OUTCOME: Blood samples were taken after 1 hour and hourly for Group 3 until 4 hours into surgery - TNFa and IL-6 levels were measured.

Results:

- PRIMARY OUTCOME: intraoperative serum IL-6 and TNFa levels after preincision and repeated doses of IV ketamine
    - No differences between the three groups at baseline
    - Group 2 and 3 showed marked drop in IL-6 after 1 hour (from 1089.54 ± 85.54 to 506.890 ± 25.34 pgm/ml in Group 2 and from 1150.27 ± 65.74 μ/ml to 586.09 ± 5.45 phb/ml in Group 3; $p < 0.05$)
        - Group 2 IL-6 levels increased slightly over consequent hours while Group 3 IL-6 levels kept decreasing during this same time ($p<0.05$)
- OTHER NOTABLE FINDINGS:
    - Group 2 and 3 showed significant decrease in TNFa serum levels, with decrease in Group 3 being significantly more ($p<0.05$) - Group 2 TNFa levels started to rise after 3 hours into surgery

Major Caveats:

- Follow-up of IL-6 levels was only intraoperatively - did not look at whether this decrease in IL-6 would be sustained later on and affect mortality and morbidity
- Study only included older male patients
- Unclear why they chose a slightly higher dose of ketamine (0.2mg/kg) for repeated injections in Group 3 compared to preincision dose

Bottom Line:

Preincisional single dose and repeated use of ketamine IV **intraoperatively** significantly decreased level of IL-6 in older male patients, with **repeated doses of ketamine being more effective** than a single shot

Studies demonstrating no statistically significant effects on IL-6

Title: Ketamine does not inhibit interleukin-6 synthesis in hepatic resections requiring a temporary porto-arterial occlusion (Pringle manoeuvre): a controlled, prospective, randomized, double-blinded study

First author: Bonofiglio, F.C.

Published in: HPB (International Hepato-Pancreato-Biliary Association) 2011

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3210972/

Research question: To determine the effect of ketamine on IL-6 levels in liver resections patients

Type of study: RCT

Key methodological points:

- > 21yrs of age with planned liver resection with the Pringle manoeuvre lasting 30-60min.
- Excluded those with chronic illnesses or other comorbidities.
- Two randomized groups, one received 0.25 mg/kg ketamine (n=21) and the other the same amount of saline (placebo, n=17).
- Serum [IL-6] obtained at baseline, 4, 12, 24, 72, & 120 hrs.

Results:

- Mean age of Ketamine group was 62 and Placebo was 54.5.
- No significant differences in [IL-6] between the groups at any point in time, although ketamine group had slightly lower [IL-6] at 4, 12, 24, 72hrs.
- Both groups had elevated [IL-6] that became almost undetectable by day 5.
- There was no major morbidity and no mortality in either group.

Major caveats: Double blinded study, but has low N, and patients with other comorbidities and chronic illnesses were excluded. This was ranked “medium quality” based on another meta-analysis.

Bottom line: Ketamine **does not seem to influence plasma levels of IL-6** in patients undergoing liver resection.

Title: A randomized, double blind, placebo controlled clinical trial of the preoperative use of ketamine for reducing inflammation and pain after thoracic surgery.

First author: *D'Alonzo*
Published in: 2011
Link: https://link.springer.com/article/10.1007/s00540-011-1206-4

Research question: Does administration of IV Ketamine during thoracic surgery decrease the inflammatory cascade and subjective pain response?
Type of study: double blind, placebo controlled, RCT.
Key methodological points

- Population: 41 patients undergoing lobectomy by video-assisted thorascopic surgery or open thoracotomy.
- Key exclusion/inclusion:
  - Patients > 18 y/o
  - Exclusion= MI within 6 mo, hx of psychotic disorder, uncontrolled HTN, allergy to ketamine, acute intracranial process, uncontrolled intracranial/intraocular HTN.
- Exposure/intervention: 0.5 mg/kg ketamine bolus vs. equivalent volume normal saline IV during thoracic surgery
- Outcome measures: levels of plasma IL6 and CRP pre-induction and 24 h post surgery, verbal pain scores at 4 and 24 h post-surgery and at discharge

Results

- Primary outcome: No significant difference in IL6 or CRP levels with administration of ketamine at baseline and at 24 hours.
- Outcome relevant to today's clinical question: Ketamine did not reduce inflammatory cytokine markers or subjective pain scores after thoracic surgery.
- Other notable findings: No hallucinations postop, no difference in adverse events between groups.

Major caveats

- Patient recruitment? 40 sequential patients or hand picked?
- Anesthetic procedure was not standardized but left to discretion of the anesthesiologist.

Bottom line

- Administration of a ketamine bolus during thoracic surgery in this RCT **did not lower cytokine levels** at 24h post-op compared to the control (normal saline bolus)

Title: Effect of low-dose ketamine on inflammatory response in off-pump coronary artery bypass graft surgery

First author: *Cho*
Published in: 2009
Link: https://www.ncbi.nlm.nih.gov/pubmed/19028707

Research question: Does administration of ketamine during off-pump coronary artery bypass graft surgery reduce the expression of inflammatory cytokines CRP, IL6, TNFa and cardiac enzymes?
Type of study: RCT
Key methodological points

- Population: 50 patients undergoing elective, isolated multi-vessel off-pump coronary artery bypass graft surgery (OPCAB) between Mar-Aug 2007
- Key exclusion criteria:
  - Exclusion= >75 y/o , MI within 2 weeks, unstable angina with elevated CK-MB, pre-op serum creatinine >1.3 mg, LVEF < 40%, previous cardiac sx, previous stroke/pulmonary disease, hx of treatment with steroid or NSAIDs within 1 month, emergency operations
- Exposure/intervention: ketamine group received 0.5 mg/kg of ketamine and control group same bolus volume of normal saline during induction of anesthesia.
  - *anesthesia protocol was standardized
  - *same surgeon for all procedures
- Outcome measures: inflammatory markers (CRP, IL6, TNFa, cardiac enzymes) measured prior to induction, 4h after surgery, POD1 and POD2.

Results

- Primary outcome: no significant differences in the pro-inflammatory markers' serum concentrations and cardiac enzyme concentrations between the groups

Major caveats

- Population= off-pump cardiac bypass patients (not generalizable)

Bottom line

- Low-dose ketamine given during anesthesia induction **did not lower serum concentrations of pro-inflammatory markers** in this RCT

Effect of low-dose ketamine on post-operative serum IL-6 production among elective surgical patients: a randomized clinical trial
Luggya et al.
African Health Sciences
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5637036/

- In healthy adults undergoing elective abdominal or perineal surgery, **ketamine 0.5mg/kg** showed **non-statistically significant** attenuation of early serum IL-6 rise and reduced 24hr increase

Effect of ketamine on pro- and anti-inflammatory cytokine response in paediatric cardiac surgery: A prospective randomised controlled study
Ibrahim
Indian Journal of Anesthesia 2017

http://www.ijaweb.org/article.asp?issn=0019-5049;year=2017;volume=61;issue=7;spage=549;epage=555;aulast=Ibrahim

- In <5yo with cyanotic heart disease undergoing CPB, ketamine at doses of **2mg/kg** and **2mg/kg followed by 50mcg/kg/min** did not significantly affect IL-6, IL-8, IL-10, TNF α and CRP

Rapid inflammation modulation and antidepressant efficacy of a low-dose ketamine infusion in treatment-resistant depression: A randomized, double-blind control study
Mu-Hong
Psychiatry Research 2018
https://linkinghub.elsevier.com/retrieve/pii/S0165-1781(18)30062-3

- In otherwise health patients with major depressive disorder, **ketamine 0.2mg/kg and 0.5mg/kg** had no effects on CRP, IL-6 and TNF-a levels over time. Ketamine 0.5mg/kg group demonstrated decreased TNF-a at 40 & 240min post treatment

In vitro studies

Title: Ketamine Suppresses Proinflammatory Cytokine Production in Human Whole Blood In Vitro
First author: Kwasaki
Published in: 1999
Link:
https://journals.lww.com/anesthesiaanalgesia/Fulltext/1999/09000/Ketamine_Suppresses_Proinflammatory_Cytokine.24.aspx

Research question: Does ketamine suppress the expression of inflammatory cytokines from human blood?

Type of study: applied cell study (in vitro)

Key methodological points

- Description: Human blood treated with different concentrations of ketamine. Afterwards, cells were stimulated with lipopolysaccharide (LPS) to induce an inflammatory cascade.
- Population: blood samples from 15 healthy male patients on no medications were used.
- Exposure/intervention: cells were exposed to different concentrations of ketamine and cytokines were measured before and after.
- Outcome measures: post-exposure TNFa, IL-6 and IL-8 levels.

Results

- Primary outcome: At 6 h, ketamine significantly suppressed LPS-induced TNF-a production in a dose-dependent manner compared to the control. Ketamine concentrations 100-500 ug/mL suppressed LPS-induced IL-6 and IL-8 production compared to the control at 6/12h

Major caveats

- Control group not explained. Non-clinical study.

Bottom line: In this study on whole human blood exposed to ketamine and then stimulated to produce inflammatory markers with lipopolysaccharide, ketamine **suppressed the production of inflammatory cytokines** TNFa, IL6 and IL8 compared to the control.

Animal studies

Effects of Ketamine on Pulmonary Inflammatory Responses in Survival in Rates Exposed to Polymicrobial Sepsis
Min Yu et al.
J Pharm Pharmaceutical Sciences, 2007
https://journals.library.ualberta.ca/jpps/index.php/jpps/article/view/695/608
OBJECTIVE: Investigate effects of ketamine on inflammatory cytokines such as TNFa, IL-6 and NF-kB in lungs of rats during cecal ligation and puncture (CLP) induced sepsis, examine effects of ketamine on TLR2 and TLR3 receptor in CLP model of polymicrobial sepsis, and study effect of ketamine on survival in CLP model of sepsis
Randomized controlled animal study

Methodology:

- POPULATION: 36 adult male Sprague-Dawley rats undergoing CLP with IV ketamine 3h post-op
- INTERVENTION: Rats were randomly assigned 6 groups: sham-operation plus normal saline (control), CLP plus NS, CLP plus ketamine (0.5mg/kg),CLP plus ketamine (5mg/kg), CLP plus ketamine (10mg/kg) and sham-operation plus ketamine (10mg/kg)
  - Normal saline administered was 10mL/kg
- OUTCOME: TNFa and IL-6 levels, TLR2 and TLR4 mRNA expression and NF-kB activity of rat lungs 6 h post-CLP-induced sepsis

Results:

- PRIMARY OUTCOME:
  - Levels of TNFa and IL-6 in the lung tissue were elevated after CLP, compared with the sham control ($P<0.05$)
  - Ketamine at doses of 5mg/kg and 10 mg/kg suppressed TNFa and IL-6 elevation after experimental CLP ($P<0.05$)
    - Ketamine did not influence levels of TNFa and IL-6 in rats who did not receive CLP
- OTHER NOTABLE FINDINGS
  - Ketamine (5mg/kg or 10 mg/kg) led to marked increase in survival after CLP ($P<0.05$)
  - Ketamine 5mg/kg and 10 mg/kg inhibited elevation of NF-kB activity after CLP ($P<0.05$)
  - Ketamine inhibited pulmonary TLR2 expression of CLP rats in dose-related manner, with minimal required ketamine dosage to be 5 mg/kg ($P<0.05$)
  - Ketamine at all doses inhibited TLR4 expression after CLP ($P<0.05$)
  - Ketamine alone did not have an effect on TLRs in rats without CLP

Major Caveats:

- Doses of ketamine 5mg/kg and 10mg/kg used in this study are relatively high compared with doses used in anesthesia of humans
- Looked at GI-induced sepsis, may potentially differ for respiratory-induced sepsis

Bottom Line:

- IV ketamine able to **suppress inflammatory cytokine production**, with improved survival in rats with **GI-induced sepsis**
- Suggests that ketamine may offer advantages during sepsis, potentially applicable to humans