Clinical Trial/Experimental Study

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A randomized controlled trial for measuring effects on cognitive functions of adding ketamine to propofol during sedation for colonoscopy

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Background

- Colonoscopy is a highly accurate diagnostic technique for large intestine and colon disease
- Sedation during colonoscopy procedure is widely used to alleviate patients *anxiety, fear, and pain*
- *Goal of sedation* : facilitate the endoscopy, sedation may also result in undesired side effect such as cognitive impairment

Background

- Propofol [ultra-short-acting sedative agent]
  - Rapid recovery profile
  - Alone >> higher cost, deeper sedation, adverse effect
  - Adjuvant >> reduce dosage, improve patient comfort

Background

- Ketamine [NMDA antagonist]
  - Sedation, analgesia, and amnesia without causing respiratory depression
  - In abdominal, orthopedic, or cardiac surgery
    - Bolus of ketamine at induction >> 65% decrease risk POCD
    - *Ketamine/propofol admixture has reduce effect of cognitive function compared with propofol in colonoscopy is not know*

Background

The purpose of this study

- Evaluate the effect of adding ketamine to propofol on cognitive functions in patients undergoing sedation for colonoscopy

Methods

Design

- Randomized, Double-blind, and controlled study
- Approved by the Ethics Committee of the First People's Hospital of Lianyungang, China
- Informed consent from all patient

Methods

Participants

- Inclusion criteria
  - Elective colonoscopy
  - Age above 18 years old
  - ASA I to II

Methods

Exclusion criteria

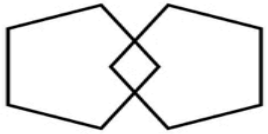
- Refuse to participate
- MMT score < 26
- Advance cardiopulmonary or phychiatric disease
- BMI > 30 kg/m^2
- Hx. Undergoing anesthesia in 7 days
- Allergy to the drugs studied

MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

Hospital Number:

One point for each answer	DATE:		
ORIENTATION Year Season Month Date Time	...../ 5	...../ 5	...../ 5
Country Town District Hospital Ward/Floor	...../ 5	...../ 5	...../ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../ 3	...../ 3	...../ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 65. (Alternative: spell "WORLD" backwards: DLROW).	...../ 5	...../ 5	...../ 5
RECALL Ask for the names of the three objects learned earlier.	...../ 3	...../ 3	...../ 3
LANGUAGE Name two objects (e.g. pen, watch).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 1	...../ 1
COPYING: Ask the patient to copy a pair of intersecting pentagons 	...../ 1	...../ 1	...../ 1
TOTAL:	...../ 30	...../ 30	...../ 30

MMSE scoring

24-30: no cognitive impairment
18-23: mild cognitive impairment
0-17: severe cognitive impairment

Methods

- Primary outcome
  - Different in accuracy on CogState test between the discharge and baseline between 2 groups
- Secondary outcome
  - OAA/S scores
  - BIS
  - MAP
  - Complications [respiratory depression, hypotension]

CogState brief computerized test battery

1. Detection

   “ Has the card turn over ”

2. Attention

   “ Is the card red? ”

3. Visual memory

   “ Have you seen this card before on this task ”

4. Working memory

   “ Is the card the same as the previous card ”

OAA/S scores

- Observer's Assessment of Alertness/Sedation score

Table 1. Observer Assessment of Alertness/Sedation Scale (OAA/S) [6]

Level of responsiveness	Speech	Facial expression	Eyes	Score
Responds readily to name spoken in normal tone	Normal	Normal	Clear, No ptosis	5
Lethargic responses to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking				1

Methods

- Patient were randomized into two group by computer
  - Group KP [ketamine/propofol]
  - Group P [propofol]
- Solution was prepared 20 ml
  - Group KP [ketamine 50 mg/ml diluted with 5% glucose up to 10 ml, mixed 10 ml of 1% propofol >> ratio 1:2]
  - Group P [10 ml 5%glucose mixed with 10 ml of 1% propofol]

Methods

- Anaesthesiologist, surgeon, nursing staff and patients were *blind* to the group assignment

Sample size

- Sample size calculation base on pilot study
- 76 patients were required each group
  - P value 0.05, Power of 80 %

Study protocol

- Dermographic data and CogState brief computerized were record before procedure
- At endoscopy room
  - IV access
  - Oxygen 4 LPM via plastic mask
  - NIBP, EKG, Peripheral O_2 sat monitoring
  - BIS at forehead

Study protocol

- All patient received 2 ml of Lidocaine IV to lesson pain on injection
- KP group : 0.1 ml/kg of solution [0.25 mg/kg of ketamine and 0.5 mg/kg of propofol] in 30 sec
- P group : 0.1 ml/kg of solution [0.5 mg/kg of propofol] in 30 sec

Study protocol

- Level of sedation was assessed [OAA/S score]
  - Maintain at level 3 [response only after nameis called loudly and/or repeatedly]
- Oxygen saturation, heart rate, and arterial blood pressure record q 5 mins

Study protocol

- After start
  - Bolus propofol 0.5 mg/kg to both group
    - BIS value > 80
    - OAA/S score > 3
- Total propofol dose were calculated and record

Study protocol

- Record
  - Respiratory depression [SpO_2 < 90% or rate < 10/min]
  - Hypotension [decrease > 20% from baseline]
  - Bradycardia [HR < 50 bpm]
  - Postprocedural pain, Postoperative vomiting
  - Duration of procedural
  - Time until OAA/S = 5
  - Time in PACU

Study protocol

- Before discharge
- The CogState brief computerized test battery
  - Detection “ Has the card turn over ”
  - Attention “ Is the card red? ”
  - Visual memory “ Have you seen this card before on this task ”
  - Working memory “ Is the card the same as the previous card ”

Statistical analysis

- The data express as the mean ± SD,IQR
- Unpaired two-tailed *t* test ; compare continuous variables between groups
- Chi-square test : category data between groups
- SPSS; version 17.0

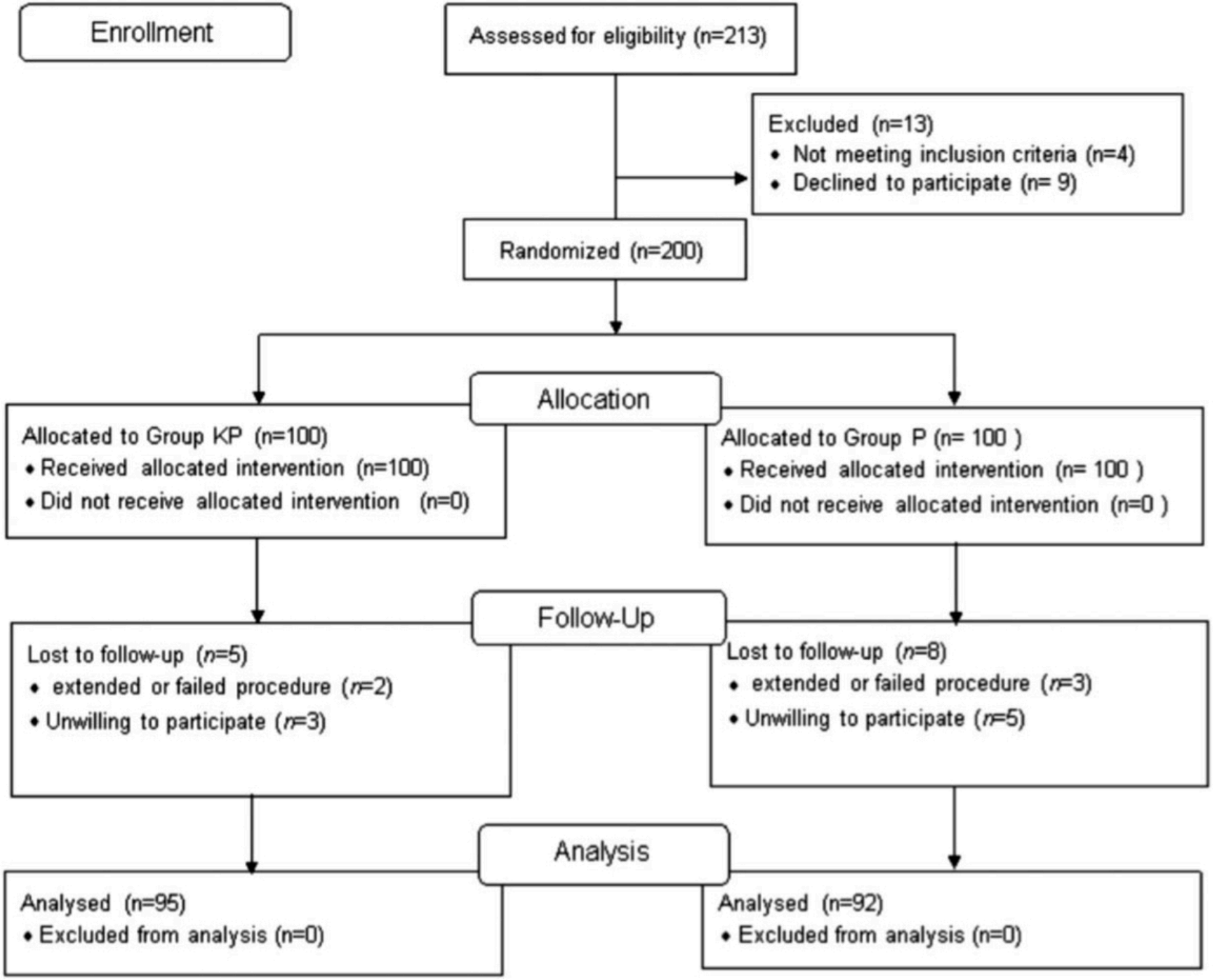


Figure 1. Consolidated Standards of Reporting Trials diagram.

Result

Table 2

Comparison of demographics, baseline monitoring (HR, MAP, SPO_2, BIS) between the 2 groups.

Demographic	Group KP (n = 95)	Group P (n = 92)	*P*
Age, yr	45.7 ± 13.9	43.4 ± 14.3	.406
Weight, kg	68.1 ± 12.3	65.5 ± 11.3	.281
Sex (F/M)	36/59	42/50	.746
ASA (I/II)	58/37	61/31	.544
HR, pulse/min	77.6 ± 15.2	74.1 ± 16.5	.271
MAP, mm Hg	90.8 ± 10.1	87.9 ± 11.9	.193
SPO_2 (%)	98 (96,100)	98 (95,100)	.622
BIS	97 (92.99)[95.98]	97 (93.99)[96.98]	.818

Data presented as mean ± SD (normally distributed data), median (range) [interquartile range](skewed data), or number (%) (categorical data). ASA = American Society of Anesthesia; BIS = bispectral index; HR = heart rate; KP = ketamine-propofol; MAP = mean arterial pressure; P = propofol, SPO_2 = oxygen saturation.

Result

Table 1

Cognitive testing baseline and discharge.

Cognitive task	Group	Baseline	Discharge	*P*
Detection (log_{10}ms)	KP (n=95)	2.55±0.10	2.61±0.11	<.001
	P (n=92)	2.56±0.11	2.60±0.12	.003
Identification (log_{10}ms)	KP (n=95)	2.73±0.09	2.77±0.10	.005
	P (n=92)	2.72±0.08	2.77±0.09	<.001
One-card learning (arcsine)	KP (n=95)	0.85±0.13	0.8±0.12	.006
	P (n=92)	0.84±0.12	0.83±0.11	.316
One-back memory (arcsine)	KP (n=95)	1.15±0.22	1.09±0.18	.040
	P (n=92)	1.15±0.23	1.13±0.21	.581

Cogstate tasks reported as mean±SD. log_{10}ms=milliseconds log transformed; arcsine=proportion correct arcsine transformed. An increase in reaction time (detec
accuracy (one-card learning and one-back memory) indicate impairment.

Result [primary outcome]

Table 4

Change of cognitive function from baseline to discharge.

Cognitive task	Group P (n = 95)	Group KP (n = 92)	*P*
Detection (log_{10}ms)	0.07 ± 0.10	0.05 ± 0.13	.201
Identification (log_{10}ms)	0.04 ± 0.11	0.05 ± 0.08	.370
One-card learning (arcsine)	(−0.05) ± 0.14	(−0.02) ± 0.09	.044
One-back memory (arcsine)	(−0.06) ± 0.1	(−0.02) ± 0.13	.028

Cogstate tasks reported as mean ± SD. log_{10}ms = milliseconds log transformed; arcsine = proportion correct arcsine transformed. An increase in reaction time (detection and
accuracy (one-card learning and one-back memory) indicate impairment.

Result

- *Primary outcome*
  - P group : impairment in psychomotor and attention
  - KP group : impairment in all 4 Test
- Group KP >> Significant reduction in
  - One card learning task [P = 0.044]
  - One back memory task [P = 0.028]

Table 3

Sedation, procedure, and recovery characteristics.

Characteristics	Group KP (n = 95)	Group P (n = 92)	*P*
Colonoscopy time, min	16 ± 6.4	14.6 ± 6.3	.281
Total propofol dose, mg	142.9 ± 22	189.7 ± 27.9	.004
Median BIS	62 (28,89)[54,71]	63 (32,85)[55,70]	.493
5 min MAP	82.3 ± 13.7	75.4 ± 16.7	.005
Respiratory depression	7/88	17/75	.023
Hypotension	10/85	22/70	.015
Bradycardia	4/91	5/87	.878
Postprocedure pain	15/80	19/73	.388
Postoperative vomiting	2/93	3/89	.970
Endoscopists highly satisfied	84/11	80/12	.760
Patient highly satisfied	93/2	88/4	.384
Time until OAA/S = 5	3.7 ± 2.4	3.5 ± 2.2	.473
Time in PACU	19.7 ± 7.5	17.8 ± 7.3	.250
Time until hospital discharge	36.1 ± 12.3	33.8 ± 11.5	.173

Data presented as mean ± SD (normally distributed data), median (range) [interquartile range](skewed data), or number (%) (categorical data). Duration of colonoscopy = time from endoscope insertion to endoscope removal. Oxygen saturation, heart rate, arterial blood pressure were recorded every 5 minutes during sedation. OAA/S score were test every 1 minute. 5 Min MAP = 5 minute after induction. Respiratory depression (rate <10/min or SPO2 <90), hypotension (a decrease of 20% in MBP compared with initial values), bradycardia HR <50/min. Satisfaction measured on 5-point Likert scale from 1 = very dissatisfied to 5 = very satisfied. For sedation satisfaction those highly satisfied = number (%) who scored 4 or 5 on Likert scale. Time until OAA/S = 5, time from endoscope removal to OAA/S = 5, time in PACU = time from endoscope removal to PACU discharge.

Result

- *Secondary outcome*
- Group KP
  - Total propofol dose significant reduce [P = 0.04]
  - 5 min MAP were higher [P = 0.05]
  - Less suffer Respiratory depression [P = 0.23]
  - Less suffer Hypotension [P = 0.015]

Discusssion

- Fast recovery & preservation of cognitive function is an important subject of research
- Our trial is the first directly investigate postprocedural cognitive function
- Contrary to initial hypothesis

" Ketamine plus propofol did not result in less cognitive impairment at discharge "

Discusssion

- Ketamine /propofol admixture cause more impairment on cognitive function
- Widely use ketamine/propofol for [PSA]
  - Meta-analysis of RCT >> several benefit
    - Reduce dose of propofol
    - Hemodynamic stability
    - Analgesia
    - Lower incidence of respiratory depression

Discusssion

- Ketamine /propofol admixture [1:1 ratio] better postoperative analgesia compared with propofol
- In this study : use 1:2 ratio >> no significant difference between postprocedure pain and recovery time
- This ratio showed more stable blood circulation, better sedation, and higher patient satisfaction

Discusssion

- Ketamine
  - Hwa et al : incidence of POCD was not significant influence by bolus dose of ketamine [0.5 mg/kg] after orthopedic surgery in elderly patients
  - RCT 672 patients challenged ketamine's effect in reducing postoperative cognitive impairment

    >> did not decrease delirium in older adults after major surgery

Discusssion

- There are many risk of POCD
  - Advanced age
  - Mental disorders
  - Long-term surgical interventions
  - Perioperative inflammatory response
  - Long-term sedation
  - Pain

Limitation

- In this study could not measure the long-term impacts on cognitive function due to discharge protocol
- Not able to precisely control level of anesthesia
- The difference of recovery time in postoperative might be masked by the variance of BIS level

Conclusion

- In this study, adding ketamine to propofol for sedation in colonoscopy
  - provided fewer complications
  - cause more impairment in cognitive functions
- Suggest : negative impact on cognitive functions of adding ketamine to propofol should be consider

Critical Apprasial

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Critical Apprasial

	Yes	Can't tell	No
2. Was the assignment of patients to treatments randomised?	✓		
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?			✓
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Critical Apprasial

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes ✓	Can't tell	No
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Critical Apprasial

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	?
10. How precise were the results? Were the results presented with confidence intervals?	yes

Critical Apprasial

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?	✓		✓
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?	✓ ✓		