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Original Research Article

CO-INDUCTION EFFECTS OF MIDAZOLAM, THIOPENTONE, KETAMINE WITH PROPOFOL IN GENERAL ANAESTHESIA

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ABSTRACT

BACKGROUND

This study was conducted to determine as to whether the co-induction strategy influences the overall amount of propofol required for induction, perhaps mitigating the related detrimental effects on haemodynamics.

METHODS

This hospital-based study was conducted from August 2009 to July 2011 at the Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, among 120 ASA I and II patients, aged 18 to 60, undergoing elective general and gynaecological surgeries under general anaesthesia. The study was approved by the institutional ethics committee, and the participants provided written informed consent.

RESULTS

According to the results of the paired "t" test conducted within the groups to measure heart rate at the two distinct intervals, group I and group 11 had significantly higher heart rates at the conclusion of the induction period. When the heart rates of the groups were compared before and after induction, it was seen that there were substantial differences between groups 1 and 11, I vs. III, I vs. IV, II vs. III, and II vs. IV. At the conclusion of induction, it was discovered that all groups I, II, III, and IV had significant reductions in systolic blood pressure from baseline levels. When the SBP (Systolic Blood Pressure) changes between the groups were compared before and after the induction, it was seen that there were significant differences between groups I and II, I and III, I and IV, II and III, II and IV, and III and IV. It

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was discovered that there was a substantial difference in the mean diastolic blood pressure distribution among the four groups both prior to and following induction. The diastolic blood pressure results at different time intervals for each group are shown in the paired "t" test results, which show that group I vs. II, I vs. III, I vs. IV, II vs. III, II vs. IV, and III vs. IV were significant. The MAP (Mean Arterial Pressure) comparison between the study groups reveals that all four groups' "p" values were deemed significant. The study determined that there was a significant difference in MAP between groups I vs. II, I vs. III, I vs. IV, II vs. III, II vs. IV, and III vs. IV prior to and after induction. The "f" test ANOVA result showed a statistically significant difference between the groups for the total dose of propofol. With a 'p' value of less than 0.05, groups II, III, and IV use less propofol than group I.

CONCLUSION

While all three co-induction drugs provide some degree of haemodynamic stability, ketamine has the best cardiovascular stability and also reduces the amount of propofol needed for induction to the greatest extent.

KEYWORDS

Co-Induction Effects, Midazolam, Thiopentone, Ketamine, Propofol.

INTRODUCTION

In recent times, propofol has been utilized as a viable substitute for the well-established thiopentone in intravenous induction of anaesthesia. Compared to thiopentone sodium, propofol induction is smoother, nearly as quick, has quicker awakening and orientation times, better intubating circumstances, and maintains upper airway integrity.[1] However, a significant drop in systolic blood pressure and its high cost are the main drawbacks of fast induction with propofol.2. When anaesthesia is induced with 2 mg/kg body weight of propofol, there are reductions of 26-28% in systolic blood pressure, 19% in diastolic blood pressure, and 11% in mean arterial pressure without alterations in stroke volume or cardiac output.[2,3] Co-induction of anaesthesia is a concept that involves giving small doses of sedatives or other anaesthetics to improve haemodynamic stability, lower the dose requirement of the induction agent, and improve the quality of anaesthesia while saving money on pricy inducing agents like propofol. Numerous co-induction methods, including ketamine, opioids,[4] barbiturates like thiopentone sodium,[5] benzodiazepines like midazolam,[6] and barbiturates like opioids, have been studied.[7] Given the current widespread use of propofol in the induction of anaesthesia, we have undertaken this study to determine whether the co-induction strategy influences the total amount of propofol required for induction, perhaps reducing the related detrimental effects on haemodynamics.

Aims and Objectives

- To assess the induction dose requirement of injection propofol.
- To observe the effects on cardiovascular stability, if any.

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METHODS

This hospital-based study was carried out from August 2009 to July 2011 at the Department of Anaesthesiology, Regional Institute of Medical Sciences, Imphal, Manipur, among 120 ASA I and II patients, aged 18 to 60, undergoing elective general and gynaecological surgeries under general anaesthesia. The study was approved by the institutional ethics committee, and the participants provided written informed consent.

Exclusion Criteria

The current trial excluded patients with substantial medical and psychiatric histories, allergies to any of the medicines to be utilized, opioid or analgesic usage during the previous 48 hours, and benzodiazepine use.

Statistical Methods

The heart rate, systolic and diastolic blood pressure, mean arterial pressure, and total dose of propofol needed to induce anaesthesia were among the various data that were obtained. These were calculated using the independent and paired "t" tests, as well as the ANOVA and chi-square tests when appropriate and required.

RESULTS

Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I	Before induction	84.30±18.08	29	3.64	0.001	Significant
	At the end of induction	90.70±17.98				
II	Before induction	85.00±17.77	29	2.73	0.011	Significant
	At the end of induction	89.70±16.59				
III	Before induction	88.37±14.96	29	1.02	0.32	Insignificant
	At the end of induction	90.63±12.70				
IV	Before induction	89.77±23.04	29	1.63	0.11	Insignificant
	At the end of Induction	93.57±18.30				
Result of Paired "T" Test within the Groups for Heart Rate Different Time Intervals						
Groups	**Time**	**Mean ± S.D**	**DF**	**T-Value**	**P-Value**	**Remarks**
I vs. II	Before induction	84.65±17.77	59	4.53	0.000	Significant
	At the end of induction	90.20±17.16				
I vs. III	Before induction	86.33±16.58	59	3.03	0.004	Significant
	At the end of induction	90.67±15.43				
I vs. IV	Before induction	87.03±20.71	59	3.50	0.001	Significant
	At the end of induction	92.13±18.04				

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II vs. III	Before induction	86.32±16.36	59	2.87	0.006	Significant
	At the end of induction	90.30±14.75				
II vs. IV	Before induction	86.98±20.36	59	3.33	0.001	Significant
	At the end of induction	91.70±17.37				
III vs. IV	Before induction	89.07±19.27	59	1.90	0.063	Insignificant
	At the end of induction	92.10±15.69				
Results of Paired "T" Test between Groups for Heart Rate at Different Time Intervals						
Table 1						

The outcome of the paired "t" test for heart rate at the two distinct intervals within the groups. It shows that, with a "p" value of less than 0.05, there was a significant rise in heart rate in group I at the conclusion of the induction. Once more, group II exhibits a notable rise in heart rate after the conclusion of induction, with a "p" value of < 0.05. Groups III and IV show a statistically negligible rise in heart rate from the baseline value, with a 'p' value of <0.05 in each group. Compared to groups I and II, groups III and IV maintained the heart rate stability more.

All four groups experienced an increase in mean heart rate, with the control group seeing the greatest increase and group III, the thiopentone-propofol group, experiencing the least increase in heart rate from the baseline value at the conclusion of induction.

A comparison of heart rates between the groups both prior to and following induction is displayed. When compared to the use of propofol alone, group I's heart rate increase was found to be statistically significantly higher than group II's, indicating that midazolam does provide some heart rate stabilization. The same pattern can be observed when comparing the heart rates at two different intervals while propofol is used alone or in combination with ketamine; group IV exhibits less change in heart rate than group I. This is also the case with group III, where we see that thiopentone stabilizes the heart rate better than propofol alone. In all groups, the 'p' values are > 0.05. The heart rate increase in group II is statistically significant compared to groups III and IV ('p' value < 0.05), indicating that thiopentone and ketamine are more effective in stabilizing heart rate than midazolam and propofol. Finally, after comparing the heart rate increases between groups III and IV, it was discovered that there was no statistically significant difference between the two groups, with both having a "p" value > 0.05. Groups III and IV had the strongest heart rate stability, with thiopentone and ketamine demonstrating greater stability in relation to heart rate changes than either propofol used alone or in conjunction with midazolam.

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Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I	Before induction	128.33±16.61	29	4.02	0.000	Significant
	At the end of induction	117.13±15.91				
II	Before induction	133.43±14.19	29	7.27	0.000	Significant
	At the end of induction	116.93±9.80				
III	Before induction	130.43±15.85	29	8.08	0.000	Significant
	At the end of induction	111.70±11.83				
IV	Before induction	128.93±14.62	29	6.28	0.000	Significant
	At the end of induction	118.33±9.94				

Result of Paired "T" Test within the Groups for Systolic Blood Pressure at Different Time Intervals

Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I vs. II	Before induction	130.88±15.53	59	7.63	0.000	Significant
	At the end of induction	117.03±13.10				
I vs. III	Before induction	129.53±15.99	59	8.17	0.000	Significant
	At the end of induction	114.40±14.17				
I vs. IV	Before induction	128.63±15.51	59	6.74	0.000	Significant
	At the end of induction	117.73±13.17				
II vs. III	Before induction	132.08±14.82	59	11.14	0.000	Significant
	At the end of induction	114.30±11.10				
II vs. IV	Before induction	131.18±14.46	59	9.32	0.000	Significant
	At the end of induction	117.63±9.82				
III vs. IV	Before induction	129.83±14.98	59	9.87	0.000	Significant

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	At the end of induction	115.00±14.65				

Results of Paired "T" Test between Groups for Systolic Blood Pressure at Different Time Intervals

Table 2

After the induction period, all study groups I, II, III, and IV had substantial reductions in systolic blood pressure from baseline levels, with 'p' values <0.05 in each group.

The four groups' respective systolic blood pressure distributions both before and after induction. The thiopentone-propofol group, group III, exhibits the greatest systolic blood pressure decline, while the ketamine-propofol group, group IV, exhibits the least amount of it.

The evaluation of variations in SBP between groups both prior to and following induction. The data indicates that there was a statistically significant drop in heart rate in group I compared to group II. This suggests that midazolam may provide some SBP stabilization when compared to propofol alone. Similarly, when we compare the SBP at two different intervals while propofol is used alone and in combination with ketamine, we see that thiopentone stabilizes the SBP better than propofol alone. Group IV exhibits significantly less change in SBP than group I. In all groups, the 'p' values are < 0.05. With a "p" value < 0.05, group II's SBP drop from baseline values is more significant than groups III and IV's, indicating that thiopentone and ketamine stabilize SBP more effectively than midazolam and propofol. In conclusion, a statistically significant difference ('p' value < 0.05) was seen in the decrease of SBP between groups III and IV. Here, it is demonstrated that, in comparison to the other study groups, the ketamine-propofol group (group IV) has the least degree of SBP decline and is hence more stable with regard to SBP changes.

Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I	Before induction	82.50±12.05	29	2.71	0.011	Significant
	At the end of induction	76.77±10.57				
II	Before induction	88.00±9.27	29	5.60	0.000	Significant
	At the end of induction	79.40±10.58				
III	Before induction	85.63±12.11	29	5.16	0.000	Significant
	At the end of induction	73.60±10.67				
IV	Before induction	84.57±10.35	29	5.41	0.000	Significant
	At the end of induction	77.40±7.91				

Result of Paired "T" Test within the Groups for Diastolic Blood Pressure at Two Different Intervals

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Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I vs. II	Before induction	85.25±11.02	59	5.47	0.000	Significant
	At the end of induction	78.08±10.57				
I vs. III	Before induction	84.32±11.95	59	5.64	0.000	Significant
	At the end of induction	75.17±10.67				
I vs. IV	Before induction	83.53±11.19	59	5.20	0.000	Significant
	At the end of induction	77.08±9.26				
II vs. III	Before induction	87.07±10.53	59	7.52	0.000	Significant
	At the end of induction	76.48±10.95				
II vs. IV	Before induction	86.28±9.89	59	7.80	0.000	Significant
	At the end of induction	78.40±9.32				
III vs. IV	Before induction	85.35±11.00	59	7.18	0.000	Significant
	At the end of induction	75.48±9.53				

Result of Paired "T" Test between Groups for Diastolic Blood Pressure at Different Time Intervals

Table 3

In all four groups, there was a considerable reduction in the DBP (Diastolic Blood Pressure). 'P' values for each group were < 0.05.

The distribution of mean diastolic blood pressure in the four groups both prior to and during induction. It demonstrates that group IV, the ketamine–propofol group, had the least amount of a reduction from the preinduction levels.

When the groups are compared to one another, it can be seen that group I had a greater fall in DBP than group II, and this difference is statistically significant ('p' value < 0.05). Comparing midazolam to propofol alone reveals that midazolam does provide some stability for DBP. A similar pattern is observed when comparing the DBP at two distinct intervals when propofol is taken alone and in combination with ketamine. This is also the case with group III, where we observe that thiopentone stabilizes the DBP better than propofol alone. Compared to group I, group IV's DBP changes less. In all groups, the 'p' values are less than 0.05. Group II experienced a greater drop in DBP compared to groups III and IV ('p' value < 0.05), indicating that thiopentone and ketamine are more effective in stabilizing DBP than midazolam and propofol. Finally, comparing the DBP changes between groups III and IV, it is discovered that there is a statistically significant difference in the DBP drop between the two groups ('p' value < 0.05). Group IV exhibited the best stability in DBP, with ketamine demonstrating the highest stability in relation to fluctuations in DBP compared to the other three study groups.

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Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I	Before induction	98.76±13.13	29	3.69	0.001	Significant
	At the end of induction	90.22±11.91				
II	Before induction	103.14±9.92	29	6.72	0.000	Significant
	At the end of induction	91.91±9.80				
III	Before induction	101.00±11.71	29	7.24	0.000	Significant
	At the end of induction	86.27±10.56				
IV	Before induction	99.36±11.44	29	6.22	0.000	Significant
	At the end of induction	91.04±8.06				

Result of Paired "T" Test within the Groups for MAP (Mean Arterial Pressure) at Different Time Intervals

Groups	Time	Mean ± S.D	DF	T-Value	P-Value	Remarks
I vs. II	Before induction	100.95±11.75	59	6.93	0.000	Significant
	At the end of induction	91.07±10.85				
I vs. III	Before induction	99.88±12.39	59	7.36	0.000	Significant
	At the end of induction	88.24±11.34				
I vs. IV	Before induction	99.06±12.22	59	6.36	0.000	Significant
	At the end of induction	90.63±10.09				
II vs. III	Before induction	102.07±10.81	59	9.80	0.000	Significant
	At the end of induction	89.09±10.49				
II vs. IV	Before induction	101.25±10.78	59	9.07	0.000	Significant
	At the end of induction	91.48±8.91				
III vs. IV	Before induction	100.18±11.51	59	9.02	0.000	Significant
	At the end of induction	88.66±9.62				

Result of Paired "T" Test between Groups for Mean Arterial Pressure (MAP) at Different Time Intervals

Table 4

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When we compare the mean arterial pressure (MAP) between the study groups, we can observe that all four groups' "p" values are < 0.05, which suggests that the mean arterial pressure decrease at the end of the induction is significant.

MAP comparison between groups both prior to and following induction. Group I showed a statistically significant lower MAP than group II, suggesting that midazolam provides some MAP stability compared to propofol alone. The same picture is seen when comparing the MAP at two different intervals when propofol is used alone and in combination with ketamine; group IV shows less change in MAP than group I. Similarly, group III demonstrates that thiopentone stabilizes the MAP better than propofol alone. In all groups, the 'p' values are less than 0.05. Compared to groups III and IV, group II has a greater drop in MAP ('p' value < 0.05), indicating that thiopentone and ketamine stabilize MAP more effectively than midazolam-propofol and propofol groups. Finally, comparing the changes in MAP between groups III and IV revealed a statistically significant difference ('p' value > 0.05). Group IV had the best MAP stability maintenance. When it comes to MAP changes, ketamine-propofol is more stable than the other three study groups. Out of all the groups, group IV has the lowest MAP drop.

Groups	**Mean ± SD (in mgs)**	**ANOVA or 'F' Test Value**	**'P' Value**	**Inference**
Group I	114.00±20.44	35.15	0.000	Significant
Group II	75.33±20.63			
Group III	74.00±19.58			
Group IV	65.33±19.43			

Results of "F" Test (ANOVA) amongst the Groups for Total Dose of Propofol (mg)

Groups		**Mean ± S.D**	**DF**	**T-Value**	**P-Value**	**Remarks**
I vs. II	Group I	114.00±20.44	58	7.29	0.000	Significant
	Group II	75.33±20.63				
I vs. III	Group I	114.00±20.44	58	7.74	0.000	Significant
	Group III	74.00±19.58				
I vs. IV	Group I	114.00±20.44	58	9.45	0.000	Significant
	Group IV	65.33±19.43				
II vs. III	Group II	75.33±20.63	58	0.26	0.89	Insignificant
	Group III	74.00±19.58				
II vs. IV	Group II	75.33±20.63	58	1.93	0.06	Insignificant
	Group IV	65.33±19.43				
III vs. IV	Group III	74.00±19.58	58	1.72	0.09	Insignificant
	Group IV	65.33±19.43				

Result of Independent 'T' Test of Mean ± SD of Total Dose of Propofol (mg) between the Groups

Table 5

The entire dose of propofol's "f" test ANOVA result reveals a statistically significant difference between the groups.

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This displays the average total dose of propofol needed to achieve the study's end goal of induction and indicates that group IV, the ketamine-propofol group, required the least amount of propofol overall. To reach the induction end point, group I, the control group, needed the greatest quantity of propofol.

With a 'p' value of < 0.05, groups II, III, and IV use less propofol than group I. Groups II, III, and IV did not show a statistically significant reduction in dosage.

DISCUSSION

In our investigation, ketamine and thiopentone were more effective in maintaining heart rate stability than midazolam or regular saline. All four research groups experienced an increase in heart rate; however, the increases in the thiopentone and ketamine groups were statistically not significant ('p' values of 0.32 and 0.11, respectively). Ketamine was more effective in maintaining heart rate stability than either thiopentone or midazolam.

Moreover, the ketamine group had the best haemodynamic stability, despite the fact that the mean arterial pressure, systolic blood pressure, and diastolic blood pressure all considerably decreased in all four groups.

Groups II, III, and IV experienced a mean arterial pressure decline from baseline of 10.88%, 14.58%, and 8.37%, respectively, due to midazolam. This was most likely a phenomenon that depended on dose.

Our data indicates that all of the study medicines reduced the propofol dose. In comparison to thiopentone or midazolam, ketamine produced the greatest reduction in the induction dose of propofol and improved haemodynamic circumstances during intubation. This result is consistent with previous research.[8,9]

With respect to the control group, the total induction dose was considerably lower in groups II, III, and IV (33.92%, 35.08%, and 42.69%, respectively) ('p' value 0.00). Our findings align with those of previous research.[10,11,12,13]

The haemodynamic depression brought on by propofol may have been offset by the sympathomimetic effects of ketamine. As a result, group IV's arterial pressure changed very little from baseline (4%). The dosage may also be a factor. All of the groups showed a tendency for their pulse rates to drop following the induction, but none of them experienced severe bradycardia.

Our results are consistent with several other studies carried out by different authors. A handful have been briefly touched upon in the paragraphs that follow.

When midazolam was combined with propofol, there was no discernible improvement in cardiovascular stability or decrease in the occurrence of apnea. This discovery, which aligns with our findings, came from a study conducted by Cressy DM et al.

Numerous additional researchers have looked into how thiopentone, ketamine, and midazolam affect propofol's effects. A study on the additive interactions between ketamine and propofol was carried out by Hui TW et al. Similar to our results, which revealed that all research groups experienced changes in blood pressure and heart rate, ketamine demonstrated the best maintenance of haemodynamic stability and the greatest reduction in the amount of propofol needed for induction. Their study, like ours, found that the cardio-stimulant effects of ketamine counterbalanced the cardio-depressant effects of propofol when used together.

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Our findings are consistent with a study by Furuya A et al.[14] titled "Intravenous ketamine attenuates arterial pressure changes during the induction of anaesthesia with propofol," in which propofol was given at a dose of 2 mg/kg and ketamine was given at 0.5 mg/kg. The study also found that ketamine with propofol preserved haemodynamic stability compared with the induction of propofol alone.

A comparative analysis of propofol-ketamine and propofol-fentanyl in minor surgery was conducted by Saha K et al.[15] which is another study that corroborates our findings. They have come to the conclusion that the combination of propofol and ketamine results in improved haemodynamic stability both throughout the induction and maintenance of anaesthesia.

Similar to our findings, Srivastava U et al. study[16] found that all three co-induction agents were effective in significantly lowering the induction dose of propofol when compared to a placebo. They also concluded that ketamine had an additional benefit in improving haemodynamic stability.

However, in a different study, Jones NA et al.[17] found that while propofol predosing did not lower the induction dose of propofol in the elderly, co-induction with midazolam does. They also discovered that, when compared to placebo, neither midazolam co-induction nor propofol auto-co-induction approach increased cardiovascular stability. These findings are consistent with our study's conclusion that midazolam provided minimal improvement in haemodynamic stability.

When compared to fentanyl 1 μg/kg, Goh PK et al.[18] found that the addition of ketamine 0.5 mg/kg enhances haemodynamics, which is similar to our findings. It is also related to better LMA installation circumstances than placebo (saline).

In a different trial, Rhee KY et al.[19] gave midazolam as a bolus at a dose of 0.02 mg/kg, then gave one group an infusion of propofol with a fixed target concentration of 1.0 μg/ml while the second group only received an infusion of propofol with an initial target plasma concentration of 2.5 μg/ml. Again supporting our conclusion on midazolam, they have shown that the combination of propofol and midazolam requires a lower total dose of propofol when compared to propofol alone, but otherwise has no greater haemodynamic stability.

Numerous investigations have previously demonstrated that midazolam is a poor coinduction agent with propofol in terms of haemodynamic stability. Minaxi HS et al. studied the effects of pre-administering midazolam 2 mg or propofol 30 mg on the induction properties of propofol.[20] The sole apparent benefit of midazolam appears to be that, like in our study, it lowers the propofol induction dose. They came to the conclusion that predosing with midazolam or propofol was just as successful at lowering the necessary induction dose, as well as the time and expense of the induction dose of propofol.

Although the amount of propofol needed to induce anaesthesia was found to be 52% lower in the presence of midazolam ($p < 0.01$), Short TG, Chui PT[21] discovered. Like the individual drugs, the combination also reduced arterial pressure at induction; in other words, midazolam did not provide haemodynamic stability in a manner comparable to what we found.

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Out of all the findings by other authors that are comparable to ours, only one study (by Ong EL and Osborne GA) has reported that low-dose ketamine at 0.3 mg/kg does not lessen the propofol induction dose or ameliorate the pain following oral surgery.[22] Here, ketamine (0.3 mg/kg) was given to the patients in the ketamine group (n = 20) before propofol (300 ml/h) was used to induce unconsciousness. Twenty individuals in the control group were given an equivalent volume of regular saline. Their conclusion differs from ours. This might be a result of the extremely low dosage of propofol they used.

In our investigation, the end aim of induction-loss of verbal contact or loss of the eyelash reflex-reduces the induction dose of propofol significantly when modest doses of ketamine, midazolam, or thiopentone are administered prior to the induction. By acting as a sympathomimetic cardiostimulant, ketamine counteracts the cardiodepressant effects of propofol and almost completely eliminates the amount needed for induction. Ketamine causes the greatest reduction in the propofol induction dose. Propofol's induction dose requirement is not as greatly reduced by midazolam as it is by thiopentone or ketamine. Thiopentone is not as effective as ketamine in counteracting the cardiodepressant effects of propofol because it itself depresses the circulatory system. Better haemodynamic stability is an extra benefit of ketamine.

We can thus confidently draw the conclusion that, of the three medications, ketamine provides the most satisfactory control of steady haemodynamic and dose decrease of propofol compared to midazolam, thiopentone, or saline based on our findings and the identical findings of numerous other scientists.

We haven't looked at the pain management, post-operative recovery, or long-term effects on psychomotor performance after co-induction with the different medications. Further research on these could lead to the discovery of a more effective co-induction combo.

CONCLUSION

We found that while all three co-induction drugs provide some degree of haemodynamic stability, ketamine has the best cardiovascular stability and also reduces the amount of propofol needed for induction to the greatest extent. However, further research is necessary to ascertain the effectiveness of co-induction medications in reducing pain and promoting a complete recovery from anaesthesia in conjunction with propofol.

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