INDUCTION AND MAINTENANCE OF ANAESTHESIA BY TWO DIFFERENT INTRAVENOUS ANALGESIC AND SEDATIVE COMBINATION WITHOUT USE OF VOLATILE AGENTS- A CONTROLLED COMPARATIVE CLINICAL STUDY IN DIABETIC AND HYPERTENSIVE PATIENTS

Ajay Kumar[1], Rashmi Taneja[2], Vipin Kumar[3], Parul Gohil[4], Kumari Shivam[5]

[1]Assistant Professor, Department of Anaesthesia, ESIC Medical College and Hospital, Faridabad, Haryana.
[2]Assistant Professor, Department of Anaesthesia, ESIC Medical College and Hospital, Faridabad, Haryana.
[3]Senior Resident, Department of Anaesthesia, ESIC Medical College and Hospital, Faridabad, Haryana.
[4]Senior Resident, Department of Anaesthesia, ESIC Medical College and Hospital, Faridabad, Haryana.
[5]Senior Resident, Department of Anaesthesia, ESIC Medical College and Hospital, Faridabad, Haryana.

ABSTRACT

BACKGROUND

In developing country like India with limited resources we need to find ways and means of cutting the anaesthetic cost without compromising safety of patient. With the availability of various intravenous analgesics and sedatives drugs safe anaesthesia can be delivered without the use of costly volatile agents and vaporisers.

METHODS

90 Adult diabetic and/or hypertensive patients were divided into three groups of 30 each. Group I patients received inj. Morphine followed by Midazolam. Group II patients received inj. Diazepam followed by Buprenorphine. Group III patients were induced with inj. Fentanyl followed by Thiopentone sodium while maintenance of anaesthesia was achieved using halothane. Hemodynamic parameters, induction and awakening time, postoperative analgesia, and cost were statistically analyzed.

RESULTS

Hemodynamic parameters showed no significant fluctuations and stayed within the acceptable sinus range in all three groups. Induction time was short but awakening time was longer in group III as compared to other two groups. Postoperative analgesia was longest in group II and this group was cost effective too.

KEYWORDS

Balanced anaesthesia, Volatile anaesthetics, Opioids, Sedatives.

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INTRODUCTION: Balanced anaesthesia can be achieved either by using intravenous agents alone or by combination of intravenous and volatile agents. Although volatile agents are used widely to administer general anaesthesia, metabolic disturbances and organic dysfunction are reported more after their prolonged use, be it halothane, isoflurane or sevoflurane, all at a heavy price. Diabetic and hypertensive patients come frequently for surgery because of multisystem involvement by these diseases. Their inherent circulatory instability and altered biochemistry are known to be worsened by all the volatile anaesthetic so far used. Today we have such time tested intravenous agents as morphine, buprenorphine, fentanyl, diazepam and midazolam, all of which so far used mainly as analgesics, amnesics and sedatives.

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Corresponding Author:
Dr. Ajay Kumar,
#B-4, 3067, Ground Floor,
Ridge View Apartments,
Vasant Kunj, New Delhi-110070.
E-mail: ajayk17@gmail.com
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By revising the dosage and pairing the combinations of one analgesic and a sedative/amnesic, safe anaesthesia can be achieved and at a terribly cheaper cost too. Cost containment, prevention of operation theatre pollution and adequate post op analgesia are advantages that call for serious attention in favour of this technique. In developing country like India with limited resources we need to find ways and means of cutting the anaesthetic cost without compromising safety, while ensuring analgesia, amnesia, relaxation, reflex suppression and early recovery. It would also help anaesthesia in field-conditions and remote parts of the country, on account of logistic reasons. This study is planned to look into these problems and to evaluate overall effectiveness of combination of easily available narcotic analgesics and tranquillizers without using any volatile agents and hence expensive vaporizers.

METHODS: After institutional ethical committee approval this clinical trial was carried out on 90 adult diabetic and/or hypertensive patients in age group of 18-60 yrs., of either sex undergoing various surgical procedures lasting of duration 90 minutes or more. Patients posted for elective general surgical, orthopaedic, gynaecological, urological and

ENT procedures were divided into three groups of 30 each. Patients having COPD, ASA grade III and IV and with history of allergy to narcotics were excluded from the study. Patients were explained about the study and written informed consent was obtained. The patients were randomized according to a computer generated random number table into three groups according to anaesthetic induction drug used. Once the patient reached operating room, baseline recordings of blood pressure, pulse rate and respiratory rate were made and an intravenous line was secured after withdrawing blood for glucose estimation in diabetic patients. GROUP I-Patients were induced with injection Morphine (0.3mg/kg), followed by Midazolam (0.15mg/kg). GROUP II-Patients were induced with injection of Diazepam (0.3mg/kg) followed by Buprenorphine (6mcg/kg). GROUP III -Patients were induced with injection of Fentanyl (2mcg/kg) followed by Thiopentone sodium (4mg/kg). All the induction drugs were given slowly with time interval of at least five minutes between two drugs. Breathing was gently assisted by oxygen & nitrous oxide mixture in case of bradypnoea (<6/min). Muscle relaxant was given once the eyelash reflex was lost. After intubation, maintenance of anaesthesia was done with oxygen, nitrous oxide mixture and supplementary doses (one fourth of initial dose) of narcotic, tranquillizer and relaxant in Group I & II, as and when patients clinical response warranted. Whereas in Group III maintenance was done using halothane instead of tranquillizer. During anaesthesia a vigilant watch was kept on any clinical signs of lightening of anaesthesia as suspected by sudden change in HR, BP or lacrimation, sweating, chest wall rigidity or inadequacy of relaxation pointed out either by surgeon or by patients attempt to breath. At the end of procedure, the relaxant effect was reversed with neostigmine (0.05mg/kg) and atropine (0.02mg/kg). No attempt was made to antagonize the effect of opioid or benzodiazepine except in the unlikely event of a severe respiratory depression.

The various parameters recorded were the induction time (the clinical end point being loss of eyelash and conjunctival reflexes), hemodynamic responses such as heart rate (HR) and blood pressure (BP) to intubation and incision, dose and nature of supplement anaesthetic or relaxant requirements, time taken to awakening and return of protective reflexes after reversal of neuromuscular block, time to supplement next analgesic dose in postoperative period, events such as nausea, vomiting, restlessness, confusion, respiratory depression, retention of urine or extreme pain were noted. All patients were closely monitored in post-operative recovery unit and were shifted back only when they met the recommended discharge criteria (Modified PADSS). Patients were asked the next day about any awareness or recall of events. Blood sugar levels were monitored perioperatively in diabetic patients. All patients were given Ondansetron (0.1mg/kg IV) towards the end of surgery. All the statistical analysis was performed using statistical package for social science (SPSS). Analysis of variance (ANOVA) was applied to compare the data between and within the groups for each event.

RESULTS: A total number of 90 adult diabetic and/or hypertensive patients of either sex, between 18-60 yrs., with ASA physical status I & II undergoing surgery lasting 90 min or more duration were recruited in the study.

Age distribution (Yrs.)	Group I	Group II	Group III	Total
35-40	2	2	2	6
41-45	3	6	6	11
46-50	8	11	11	27
51-55	7	6	6	20
56-60	10	5	5	26
Total	**30**	**30**	**30**	**90**

Table 1: Age distribution

Demographic studies showed that 48.8 percent of patients (44 out of 90) were between 35-50 years and 51.1% of patients (46 out of 90) were between 51-60 years of age. 46-60 years alone formed 81% (73 out of 90). Numbers are not equal due to randomized selection of patients (Table 1).

Sex	Group I	Group II	Group III	Total
Male	7	9	13	29
Female	23	21	17	61

Table 2: Sex distribution

In this study, the female preponderance (67.7%) is just a coincidence which is due to contribution by larger number of gynaecologic and gall stone patients (Table2).

Disease	Diabetic	Hypertension	Diabetic & hypertension	Total
No. of patients	42	42	6	90

Table 3: Disease wise distribution

46.6% of patients (42 out of 90) were hypertensive and 46.6% (42out of 90) were diabetic (Table 3). However, patients having both diabetes and hypertension constituted a small number i.e. 6.6% (6 out of 90).

Groups	Group I	Group II	Group III	P Value
Mean time taken (MINS)	13	14	5.5	<0.05
Range(MINS)	(10-16)	(12-22)	5.5-7	

Table 4: Shows the average time taken for induction of anaesthesia in the three groups

Induction time was longer and comparable in groups I and II (13-14min), but was reduced to less than half when fentanyl plus thiopentone combination was used (p value <0.05). (Table 4)

Time intervals	Group I	Group II	Group III	P Value
Base line	84 (62-119)	84 (66-116)	82 (56-115)	0.755
After first drug	78 (60-110)	80 (64-111)	78 (50-119)	0.625
After second drug	75 (54-101)	77 (63-110)	85 (58-120)	<0.05
After suxamethonium	80 (66-105)	82 (66-110)	88 (61-126)	0.055
After intubation	92 (75-116)	95 (77-122)	93 (60-126)	0.710
Before incision	83 (70-102)	84 (69-109)	88 (62-112)	0.261
After incision	85 (65-110)	87 (72-102)	84 (55-112)	0.416
5 Min	82 (62-110)	83 (67-97)	79 (54-120)	0.384
15 Min	80 (65-108)	81 (69-93)	77 (57-113)	0.333

Table 5: comparative study of mean HR changes in three different groups

There was consistent fall in mean heart rate in Gp I & II after giving induction agents whereas heart rate transiently increased in Gp III after thiopentone injection (p value <0.05). Heart rate increased in response to intubation was of same magnitude in all the groups. All changes were transient, falling to normal before incision and change on incision was insignificant in all groups. (Table 5)

Time intervals	Group I	Group II	Group III	P Value
Base line	133 (108-160)	134 (110-154)	133 (102-163)	0.942
After first drug	125 (102-150)	122 (96-142)	123 (96-160)	0.690
After second drug	117 (98-141)	113 (90-138)	110 (90-141)	0.141
After suxamethonium	123 (102-140)	118 (98-141)	114 (94-140)	0.051
After intubation	138 (110-160)	140 (108-170)	121 (96-170)	<0.05
Before incision	125 (106-140)	122 (90-141)	110 (90-141)	<0.05
After incision	127 (88-142)	123 (92-140)	100 (64-140)	<0.05
5 Min	123 (90-160)	121 (90-141)	115 (90-170)	0.055
15 Min	125 (102-108)	120 (92-131)	123	0.611

Table 6: Comparative study of mean SBP changes in three different groups

Administration of Morphine, diazepam, and fentanyl in their respective groups produced comparative fall in SBP. A further fall of equal intensity followed the second drug in all groups. The rise in mean SBP was noted in Gp I & II after intubation which was not comparable to Gp III where mean SBP decreased (p value<0.05). (Table 6)

Groups	Group I	Group II	Group III
Patients needed repeat dose	24	18	11
1 repeat dose	10	11	8
2 Repeat dose	11	6	2
3 Repeat dose	1	1	1
>3 Repeat dose	2	0	0

Table 7: Shows repeat dose of relaxant needed in three different groups (No. of patients)

Adjuvant relaxant requirement was least in Gp III & was comparable in Gp I & II. (Table 7)

Supplement	GP I	GP II	GP III
First drug	3(10%)	6(20%)	10(33.3%)
Second drug	25(83.3%)	4(13.3%)	-

Table 8: Patients requiring anaesthetic supplement

25% of initial dose of intravenous induction agents were given as required, clinically assessing any signs of lightening of anaesthesia by tachycardia, sudden rise in blood pressure, lacrimation, or limb movement. In group I 83.3% of patients required supplemental midazolam while only 10% required morphine. In group II 20% of patients required supplemental diazepam while only 13.3% required buprenorphine. In group III, 30% of patients needed supplemental fentanyl and there was no need of supplemental thiopentone as anaesthesia was maintained with halothane. (Table 8)

Groups	Group I	Group II	Group III	P Value
Mean time taken (In minutes)	3	2.5	7	<0.05
Range	(1-19)	(1-22)	(3-13)	

Table 9: Shows the mean time taken for awakening after reversal of relaxant in three groups (min)

The mean time taken for awakening and return of protective reflexes after reversal of relaxant was less and comparable in Gp I & II as compared to Gp III where it was prolonged (7 min) (p value <0.05). (Table 9)

Groups	Group I	Group II	Group III	P Value
Duration of analgesia (hrs)	7.5	10	4	<0.05
Range	(4-10)	(4-16)	(1-8)	

Table 10: Shows duration of post-operative analgesia (hrs)

The mean duration of Postoperative analgesia was longest in Gp II (10hrs) followed by Gp I (7.5hrs) & Gp III (3hrs) (p value <0.05). (Table 10)

Groups	Group I	Group II	Group III	P Value
Average cost (IN RS)	144	72	134	<0.05
Range	(114-149)	72	(113-173)	

Table 11: Shows the average cost of induction agents used in three groups

The average cost of drugs used was least in Gp II followed by Gp I. Considering the cost of vaporizers, group III could prove costliest. (Table 11)

Group	I	II	III
Diabetic	28.2%	25.6%	40.6%
Hypertensives	21%	18.5%	20.75%

Table 12: Comparative study of mean percentage increase in postoperative as compared to preoperative blood sugar in diabetic and hypertensive patients in different groups

The mean rise in postoperative blood sugar levels in diabetic patients as compared to preoperative levels was maximum in Gp III(40.6%) as compared to Gp I & Gp II(28.2% & 25.6%) which was statistically significant(p value<0.05). (Table 12)

DISCUSSION: This comparative clinical study has been undertaken on ninety adult patients undergoing surgery of 90 minute or more duration, to evaluate the feasibility, advantages and hazards if any, of total intravenous anaesthetic technique[1] as compared with a balanced anaesthetic technique using volatile agent in diabetic and hypertensive patients. In a prospective study of this nature, and time constraints, it was not possible to maintain equality of numbers and genders among different age groups. One may question the propriety of referring to this technique as total intravenous anaesthesia. In the absence of compressed air for positive pressure ventilation we had to use oxygen and in order to avoid the ill effects of prolonged use of 100% oxygen by IPPV, one needed either nitrogen or other inert gas. We decided to use nitrous oxide for the purpose. This was employed uniformly in all patients under study. All the patients had received identical premedication. Subsequently they were randomly divided into three equal groups depending on whether they received morphine plus midazolam (GP-I), diazepam plus buprenorphine (GP-II) or fentanyl, thiopentone plus halothane (Gp III). All patients were intubated, paralyzed and mechanically ventilated.

Heart rate changes by and large followed a comparable pattern in all three groups of patients at corresponding time intervals. In any case, there were no serious fluctuations at any time, and the rate stayed within the acceptable sinus range at all-time intervals. Intubation, rather than skin incision made a moderate rise in heart rate, and this too has been consistent in all groups.

Morphine, Midazolam, Diazepam, Buprenorphine and Fentanyl produced mild but consistent and comparable fall in heart rate, the mean fall being 4-6 beats per minute, and was not different between hypertensive and diabetic patients. There was statistically significant rise in heart rate after giving Thiopentone in group III as compared to other two groups which can be due to decrease in blood pressure that is offset by a compensatory increase in heart rate.[2] A study conducted by Filner and Karliner[3] (1976) to see the effect of intravenous thiopentone in normovolemic patients showed similar results. Skin incision produced statistically insignificant changes in all patients of all groups.

SBP as like heart rate followed a comparable pattern in all three groups of patients at corresponding time intervals. SBP showed less than 5% fall after Morphine in hypertensive and diabetic patients and close to 10% both after Diazepam and Fentanyl. Such marginal fall in SBP was also seen following Midazolam, Buprenorphine and Thiopentone. They were statistically insignificant and comparable.

Statistically significant blunting of intubation response was seen in group III as compared to other groups which can be explained by use of Fentanyl.[4,5] No pressor response was seen on surgical incision in any patient of any group, when present it was slightly depressor response only. On the whole all three drug combinations were safer as sole anaesthetic agents in hypertensive and diabetic patients.

Mean induction time was longer in group I and II but the time could be considerably curtailed by Fentanyl–Thiopentone combination to less than half. This can be explained by rapid onset of action of thiopentone.[6]

Relaxant supplement given as vecuronium was more in group I, lesser in Group II and least in group III when Fentanyl, Thiopentone and Halothane combination was used. Here the use of halothane for maintenance of anaesthesia could be held up as a reason as halothane itself has some skeletal muscle relaxation properties.[7] Supplemental midazolam requirement was maximum in group I which can be explained by short duration of action of same.

Awakening time was short in group I & II but was prolonged in group III. Patients in group I and II were sedated in recovery period but they were easily arousable, while many of the patients in group III were drowsy at recovery. This shows that recovery was better in group I and II as compared to halothane group (group III). Hence recovery time was prolonged after supplementing volatile agent over and above intravenous agents.[8]

First dose of postoperative analgesic was required early in group III (4hrs) and much later in group II (10hrs). Group I patients took 7 hours for subsequent analgesic dose suggesting the longer analgesic effect of Buprenorphine and then Morphine.[9,10]

The cost of induction and maintenance of anaesthesia was least in Diazepam-Buprenorphine group followed by Morphine–Midazolam group. The difference from Fentanyl–Thiopentone–Halothane group will be significant if the cost of vaporizer is added to it.[11]

Blood sugar could be well maintained both in diabetics and hypertensives alike by the two trial groups of TIVA. However, with diabetic patients, conventional balanced anaesthetic technique in group III proved less effective, as a mean rise by 40% in postoperative blood sugar levels was seen in diabetic patients of this group. The trial groups I &

II showed only a rise by 28 & 25% in postoperative blood sugar which was acceptable considering the rise of 18 & 21% in hypertensive patients too. Inevitably, diabetic patients present for surgery with the complications of the disease: cardiac, vascular, renal, ophthalmic etc. The metabolic management of these patients in the perioperative period has become routine. Several factors complicate the metabolic management of the diabetic patient in perioperative period. These include starvation, before and after operation, the endocrine and consequent metabolic responses to surgery and immobilisation. High dose opiate anaesthetic techniques produce not only hemodynamic, but also hormonal and metabolic stability. These techniques effectively block the entire sympathetic nervous system and the hypothalamic-pituitary axis, probably by a direct effect on the hypothalamus and higher centers. Abolition of catabolic hormonal response to surgery will, therefore, abolish the hyperglycaemia seen in normal patients and may be of benefit in the diabetic patients. Halothane, sevoflurane and isoflurane, in vitro, inhibit the insulin response to glucose in a reversible and dose dependent manner.[12]

Vomiting and retching was noted in all three groups but it was maximum in group II (Diazepam-Buprenorphine) and least in group III (Fentanyl-Thiopentone). This is due to stimulation of the chemoreceptor trigger zone, but a vestibular component is also contributory. Hence, gentleness while shifting the patients from the operation table to the trolley and thereafter would effectively eliminate the possibility of this complication arising.

Urinary retention was seen in 3(10%) patients in group I and 4(13.3%) in group II. None of the patients in group III had this problem.

None of the patients had any awareness or recall of events.

CONCLUSION: It is concluded that all three combinations of anaesthetic used were safe and feasible in hypertensive and diabetic patients. Vaporizers can be dispensed with and still can practice safe anaesthesia that too with cost effectiveness and reduced risk of Operation theatre pollution.[13]

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