Original Article

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Intravenous Dexamethasone versus Tramadol for Prevention of Shivering after General Anaesthesia: A Randomised Double Blind Placebo Controlled Trial

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Abstract

Background: Postoperative shivering is very common and followed by many complications. In most operating and recovery rooms, shivering is controlled by the use of humidifiers, warming blankets and humidified oxygen. However pharmacological control is an alternative modality. The goal of this study was to compare the effect of dexamethasone, tramadol and saline for prevention of shivering and nausea/vomiting after general anaesthesia. **Subjects and Methods:** This double blind randomised controlled study was carried out on 300 patients being operated under general anaesthesia. The patients were block randomised into three groups (n=100 each). Group D received 0.1 $mg.kg^{-1}$dexamethasone, Group T received 1 $mg.kg^{-1}$tramadol and Group C received normal saline I.V as 10 ml solution just after endotracheal intubation. Temperature monitoring was done. In the recovery room, all patients were continuously observed for occurrence of shivering, nausea and vomiting. Quantitative parameters were compared by unpaired t-test and qualitative parameters by Chi-square / Fisher's exact test. Hemodynamic parameters were compared using repeated measure ANOVA. **Results:** The incidence of shivering was 23% in group D, 9% in group T and 51% in group C ($p<0.001$). In group D, 22% patients developed PONV as compared to 62% in group T and 59% in group C ($p<0.001$). **Conclusion:** Both dexamethasone and tramadol are effective anti-shivering agents with tramadol being more effective. However, since tramadol has a slightly higher clinical incidence of nausea/vomiting, dexamethasone should be the preferred anti-shivering agent in surgeries or patient subgroup who are at a higher risk of developing PONV.

Keywords: Dexamethasone, tramadol hydrochloride, anaesthesia, general, shivering, postoperative nausea and vomiting

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Introduction

Postoperative shivering is a common experience for patients operated under general anaesthesia (GA). The reasons for shivering are a reduction in the vasoconstriction threshold, redistribution of the temperature from the core to the peripheral tissues and peripheral vasodilation caused by anaesthetic drugs. The incidence of post anaesthetic shivering (PAS) has been reported to range from 60-75% in patients recovering from GA.[1] As a result of PAS, there is increased oxygen consumption and carbon dioxide production, increased heart rate and blood pressure. These effects result in exacerbation of ischemic heart disease, increase intracranial pressure, intraocular pressure and a significant decrease in mixed venous oxygen saturation. If these factors are severe enough, they can lead to hypoxia and lactic acidosis which can complicate the recovery. In addition, PAS may aggravate wound pain and delayed wound healing.[1]

Various pharmacological and non-pharmacological methods can be used to prevent and control PAS. Tramadol, a centrally acting opioid with action mainly on the μ-receptor and minimal activity on the κ- and δ-receptors, has anti-shivering activity mainly due to its opioid and serotonergic or noradrenergic activity or both.[1]However, this drug is associated with an increased incidence of postoperative nausea vomiting (PONV), which is otherwise, to the tune of 23.7% post GA, as per a large-scale study in Japan.[2] The risk may be as high as 70-80% in high risk groups.[3] So, the search for an anti-shivering agent which does not lead to an increase in the incidence of undesirable side-effects is on.

Dexamethasone, a synthetic adreno-corticosteroid with glucocorticoid activity, may have a role in reducing the PAS. The mechanism for this effect may be due to its property to

reduce the gradient between the skin and core body temperature. Another proposed mechanism of anti-shivering action is by regulating immune responses.[4] In one of the studies, dexamethasone has also been shown to be superior to pethidine as an anti-shivering agent.[5] It also has anti-emetic properties which have been reported to be comparable to ondansetron in the immediate post-operative period.[6]

According to the available literature, both tramadol and dexamethasone are effective in the prevention of PAS.[5,7,8] We hypothesized that dexamethasone would be more effective than tramadol for reducing the incidence of PAS and will have a positive impact on PONV also. Therefore the present study was planned to compare the incidence of PAS after prophylactic administration of intravenous dexamethasone ($0.1 mg.kg^{-1}$), intravenous tramadol ($1 mg.kg^{-1}$) and compare the same with intravenous saline. Moreover, the side effect profile of dexamethasone and tramadol with respect to the incidence and severity of nausea and vomiting has also been studied.

Subjects and Methods

This double blind randomized controlled trial was conducted at UCMS and GTB hospital, Delhi, after obtaining Institutional Ethics Committee approval and written informed consent from all the participants. The study was registered with ctri.nic.in before recruitment of the participants. (CTRI/2017/03/008233)

Three hundred ASA I/II patients of either sex between 18-60 years of age scheduled for elective surgical procedure of expected duration between 1-3 hours were included in this randomised controlled study. Patients with history of smoking, motion sickness, myocardial infarction, neuromuscular disorders, hypothyroidism or hyperthyroidism, diabetes, convulsions, pregnant females, preoperative oral temperature >38°C or <36°C, raised intracranial tension, on anti-depressant medications, corticosteroid therapy, allergy to study drugs or haemodynamic instability were excluded.

To avoid bias due to weather/climatic changes, block randomization technique was used to allocate patients equally to the three intervention groups. Concealment was done using sequentially numbered sealed opaque envelopes.

The study drug was prepared as a 10 ml solution in a syringe by a person not involved in the study. Both the patient and the person who was conducting the case, administering the study drug and observing the patient for the outcome measures in the post-operative period was blinded to the group allocation.

Group D: Dexamethasone $0.1 mg.kg^{-1}$ diluted with NS upto 10 ml.

Group T: Tramadol $1 mg.kg^{-1}$ diluted with NS upto 10 ml.

Group C: Normal saline 10 ml.

All patients were premedicated with tablet ranitidine 150 mg and alprazolam 0.25 mg orally night before and in the morning of surgery. In the preoperative room, baseline oral temperature was measured and recorded. Standards monitors including electrocardiography, non-invasive blood pressure monitoring, pulse-oximetry was attached in the operating room (OR). The OR temperature was recorded.

Anaesthesia was induced with morphine $0.1 mg.kg^{-1}$ i.v. and propofol $2 mg.kg^{-1}$ i.v. Vecuronium $0.08 mg.kg^{-1}$ i.v. was used to facilitate tracheal intubation. Anaesthesia was maintained with 33% N_2O in oxygen, isoflurane and intermittent top-up doses of vecuronium. After intubation a nasopharyngeal temperature probe was inserted for continuous nasopharyngeal temperature monitoring. Temperature readings were recorded immediately after intubation, just before extubation and the lowest temperature attained during intraoperative period. Study drug was administered intravenously just after induction. Neuromuscular blockade was reversed using appropriate doses of neostigmine and glycopyrrolate i.v. and the trachea was extubated. No active or passive warming devices were used intraoperatively or postoperatively.

Patients were then shifted to the recovery room where they were continuously observed for occurrence of shivering, nausea and vomiting. Severity of shivering, nausea and vomiting was graded ([Tables 1,2] respectively).[9,10] A rescue dose of pethidine 25 mg i.v. was administered to treat shivering grade $\geq$2. Ondansetron 4 mg i.v. was given to treat nausea/vomiting grade $\geq$2.

Pulse rate and blood pressure were recorded immediately after shifting to recovery room and then at half hourly intervals in the recovery room up to 2h. Any other complications occurring in the postoperative period were also recorded. Total amount of IV fluids transfused during the surgery was also recorded.

Considering the incidence of shivering as 47.5% in control group and 10% in dexamethasone group according to a previous study,[5] to estimate this difference at a error = 5% and power = 80%, a sample of 22 cases is required in each group. Similarly, considering the incidence of shivering in control group as 75% and in the tramadol group as 17.5%,[11] at a error=5% and power=80%, a sample of 11 cases is required in each group to estimate this difference. Now, to estimate the reduction in the incidence of PAS in tramadol and dexamethasone group as compared to control, we consider the reduction in tramadol as 57.5% and 37.5%in the dexamethasone group.[5,11] To estimate a similar difference in our study at a=5% and power=80%, a sample of 97 cases were required in each group. TO account for dropouts, we included 100 patients in each group.

Statistical analysis was performed using SPSS program for windows, version 20.0. One time measured quantitative parameters which followed the normal distribution were com-

pared using unpaired t-test and qualitative parameters using Chi-square / Fisher's exact test. Repetitively measured quantitative measures were compared by repeated measure ANOVA and qualitative measures by Chi-square/Fisher exact and McNemar test. Bonferroni correction was applied wherever applicable. P-value < 0.05 was considered significant.

Results

A total of 313 patients were assessed for eligibility. Six patients did not meet the inclusion criteria and seven patients declined to participate. Thus, a total of 300 patients were block randomised into three groups. Age, weight, ASA class, gender distribution and duration of anaesthesia were comparable among the three groups [Table 3].

[Table 4] shows the temperature trends of the operating room, recovery room and the patients preoperatively, immediately after intubation, before extubation and lowest temperature attained during intraoperative period. Temperature was comparable at all the time points. The temperature drop, i.e. the difference between core temperature after intubation and the lowest temperature attained intra-operatively, was also comparable in all the three groups.

Heart rate [Figure 2], systolic blood pressure and diastolic blood pressure [Figure 3] recorded in the recovery room up to 2 h was also comparable (p=0.649, p=0.718, p=0.835 respectively).

There was significant difference in the incidence of shivering and nausea/vomiting among the three groups (p<0.001; [Table 5]). [Table 6] shows the severity of shivering and nausea/vomiting in each group.

Four patients in group D and five patients each in group T and C required pethidine to control shivering. Ten patients in group D, 26 in group C and 25 in group T required ondansetron to control nausea/vomiting. All patients in three groups had a single episode of PONV except 2 patients in group D who developed a second episode. There was no difference in the requirement of rescue drug in any of the groups (p>0.05).

Discussion

Prevention and treatment of postoperative shivering and PONV form an important part of patient care after surgery. In our study we have compared the efficacy of prophylactic i.v dexamethasone 0.1 mg.kg^{-1},i.v tramadol 1 mg.kg^{-1} or saline for their effect on PAS and PONV.

We found that the incidence of shivering was significantly lower in the tramadol group compared to both dexamethasone and control groups (9% vs. 23% and 51% respectively, p<0.001) despite the ambient temperature of the OR and RR remaining comparable among the three groups. The

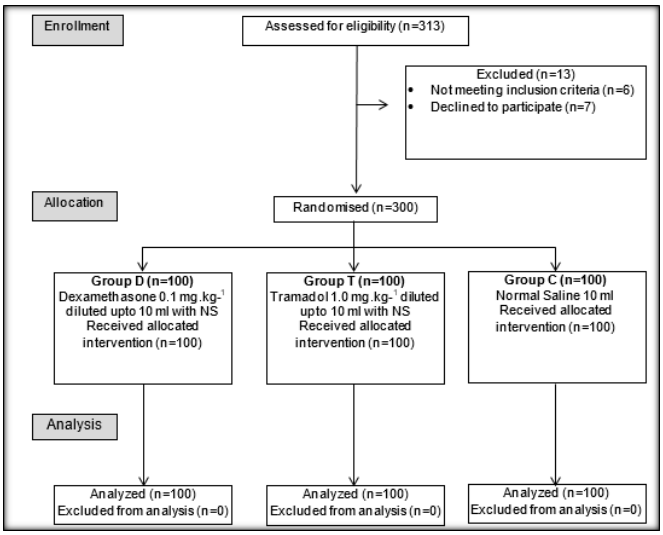

Figure 1: CONSORT flow diagram

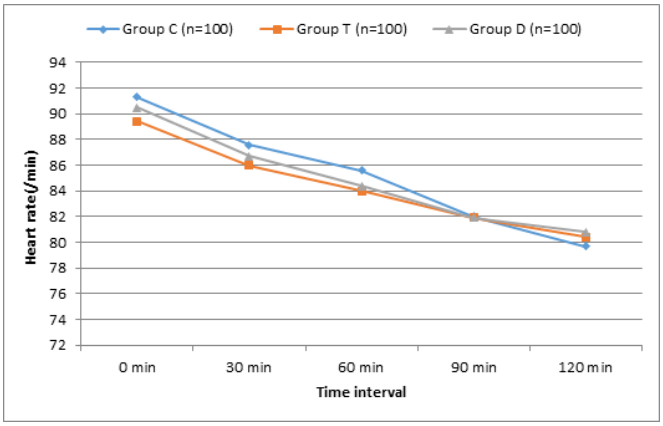

Figure 2: Heart rate in the post-operative period

temperature drop among patients in the three groups was also similar.

The efficacy of dexamethasone as an anti-shivering agent administered post-induction of anaesthesia has been proven in previous studies.[5,7,8] The study by Yared et al used dexamethasone in a very high dose (0.6 mg/kg) and was conducted on patients undergoing cardiac surgery. In this dose, the incidence of shivering was reduced from 33% in control group to 13.1% in dexamethasone group.[7] Lower dose of 0.25 mg/kg dexamethasone also proved effective in reducing shivering to 16.7% compared to 40% in control group. In this study, dexamethasone was administered prior to induction of anaesthesia.[12] Later, the study by Entezariasl M and Isazadehfar K involved patients undergoing non-cardiac surgeries where still lower dose of dexamethasone (0.1

Table 1: Grades of shivering. [10]

Grade	Clinical signs
0	No shivering
1	Mild fasciculations of face or neck and ECG disturbances in the absence of voluntary activity of the arms
2	Visible tremor involving more than one muscle group
3	Gross muscular activity involving the entire body

Table 2: Grades of nausea and vomiting. [11]

Grade	Clinical signs
0	No nausea and vomiting
1	Nausea without vomiting
2	Nausea with vomiting <3 episodes
3	Nausea with vomiting >3 episodes

Table 3: Demographic characteristics

	Group C (n=100)	Group T (n=100)	Group D (n=100)	p-value
Age (years)*	36.4±12.9	36.8±13.3	37.3±13.2	0.885
Weight (kg)*	54.7±7.1	55.5±8.0	55.8±8.2	0.556
Sex ratio (M:F)#	26:74	18:82	25:75	0.342
ASA class (I:II)#	67:33	71:29	63:37	0.485
Duration of anaesthesia (min)*	105.2±28.2	104.5±26.7	106.1±27.9	0.915

*Values expressed as mean±SD,#Values are expressed as ratio, n=number of patients.

Table 4: Temperature trends

Temperature (°C)	Group C (n=100)	Group T (n=100)	Group D (n=100)	p-value
Operating Room	24.8±1.2	24.7±1.4	24.9±1.2	0.395
Recovery Room	24.6±1.1	24.7±1.2	24.9±1.1	0.272
Preoperative	36.9±0.2	36.8±0.2	36.9±0.2	0.779
After intubation	35.8±0.5	35.8±0.7	35.8±0.6	0.896
Lowest intraop	35.4±0.5	35.4±0.7	35.4±0.7	0.934
Before extubation	35.5±0.5	35.5±0.6	35.5±0.7	0.936
Temperature drop	0.42±0.2	0.41±0.24	0.43±0.34	0.891

Values expressed as mean±SD, n=number of patients

Table 5: Incidence of shivering and postoperative nausea/vomiting (PONV)

	Group C	Group T	Group D	p-value	Pair-wise p-values
Shivering	51 (51%)	9 (9%)	23 (23%)	<0.001	C vs. T: <0.00001 T vs. D=0.006928 C vs. D=0.000041
PONV	59 (59%)	62 (62%)	22 (22%)	<0.001	C vs. T=0.664332 T vs. D<0.00001 C vs. D<0.00001

Values expressed as number (%), n=number of patients

Table 6: Severity of shivering and nausea/vomiting

		Group C (n=100)	Group T (n=100)	Group D (n=100)
Grade of shivering	0	49 (49%)	91 (91%)	78 (78%)
	1	21 (21%)	4 (4%)	18 (18%)
	2	30 (30%)	4 (4%)	2 (2%)
	3	0 (0%)	1 (1%)	2 (2%)
Grade of nausea/ vomiting	0	41 (41%)	38 (38%)	77 (77%)
	1	33 (33%)	37 (37%)	13 (13%)
	2	26 (26%)	25 (25%)	10 (10%)
	3	0 (0%)	0 (0%)	0 (0%)

Values expressed as number of patients (% of patients), n=number of patients.

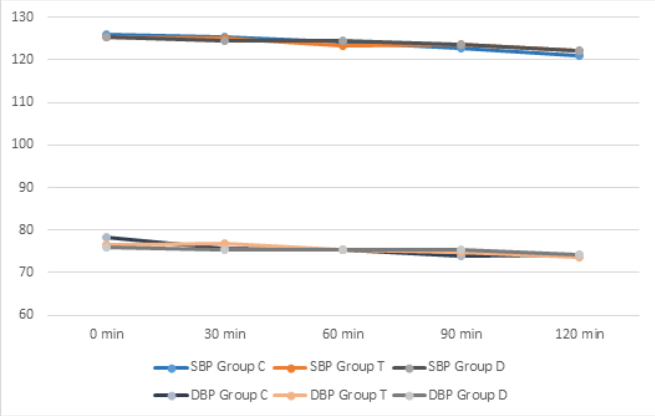

Figure 3: Systolic and Diastolic blood pressure in the post-operative period

mg.kg^{-1}) was used. The dose and timing of administration of dexamethasone in this study was similar to that used in our study. The incidence of shivering was reported to be 10% in dexamethasone group compared to 47.5% in control group. This study reported that dexamethasone was better than meperidine in controlling PAS, the incidence with meperidine being 37.5%.[5] In a randomised controlled trial on 123 patients, dexamethasone was found to be comparable to ramosetron for its anti-shivering acitivity.[13] The combination of ramosetron with dexamethasone was superior to ramosetron alone for control of PAS.[14] Our study also showed that dexamethasone is an effective anti-shivering agent as the incidence of shivering was 23% in dexamethasone group compared to 51% in the control group.

Studies have proven that tramadol is effective as prophylactic anti-shivering agent and also for its management in the postoperative period in a dose of 1 mg.kg^{-1}.[9,15] Some of these studies state the superiority of tramadol in this dose over pethidine 0.5 mg.kg^{-1}. In the present study, we observed that tramadol 1 mg.kg^{-1}was superior to control in preventing PAS (9% vs. 51% respectively; P<0.001). Not only that, the incidence of PAS was significantly less as compared to dexamethasone (9% vs. 23%). The only study comparing the anti-shivering effect of tramadol with dexamethasone and ketamine was done on 90 patients. This study reported incidence of shivering to be 13.8%, 26.7% and 40.1% respectively (p>0.05). This study was conducted on a small patient group with 30 patients in each group. The timing of administration the study drug was just before wound closure.[16] As the proposed mechanism of action of dexamethasone is modification of the immune response and thus, prevention of release of anti-inflammatory mediators,[7] the best timing of its administration should be prior to surgical incision. In our study, conducted on 300 patients, the incidence of shivering was similar to the study by Vinathi et al; 9% in tramadol group and 23% in dexamethasone group.

The incidence of PONV for the first 2 h postoperatively was found to be 59% in control group vis-à-vis 62% in the tramadol treated group and 22% in dexamethasone treated group (p<0.001). There is no direct study which has compared the incidence of PONV with tramadol and dexamethasone. However, Mohta et al,[15] and Angral et al,[11] reported no significant increase in the incidence of nausea/vomiting with tramadol compared to control. In the present study also, the incidence of PONV was comparable in the tramadol and control groups. However, there was a significant reduction in the incidence of PONV in patients who were administered dexamethasone compared to both, tramadol and saline. As per the result of the DREAMS trial on 1350 patients undergoing open or laparoscopic bowel surgery, the overall incidence of PONV was 29.3%. The incidence of PONV was significantly less in the group that had received prophylactic 8 mg i.v. dexamethasone (25.5%) compared to the control group[17] In a meta-analysis Wang et al found dexamethasone to be more effective in preventing PONV than ondansetron in late post-operative period (6-24 hours).[6]

As per a recent meta-analysis, 4 to 5 mg dexamethasone was found to be as effective as 8 to 10 mg dose for controlling PONV.[18] But, in this study, we used a dose of 0.1 $mg.kg^{-1}$based on many other studies reporting its efficacy in this dose. Another limitation of the study was that the gender bias cannot be ruled out although the gender distribution was comparable among the three groups, the overall number of females participating in the trial were more compared to males. Although we did not include ENT procedures, the large sample size excluded the possibility of restricting to only one type of surgical procedure. Lastly, since we observed the patients for the first 2 postoperative hours only, we could have missed the delayed effects of these drugs.

Conclusion

From the results of the study above, we conclude that both tramadol and dexamethasone are effective anti-shivering agents. Tramadol is more effective than dexamethasone in preventing postoperative shivering. However, an anti-emetic supplementation may be required more frequently to control or prevent nausea/vomiting with tramadol. Dexamethasone has anti-shivering properties along with anti-emetic properties. So, dexamethasone should be the preferred drug over tramadol in surgeries or patient subgroup who have a higher risk of developing PONV.

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