Comparing the efficacy of prophylactic use of hydrocortisone and low dose ketamine for prevention of shivering under spinal anesthesia

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Abstract

Introduction: The thermoregulatory system plays an important role in coordinate the defense system against the environment in regulating the normal body temperature in homoeothermic species. Hypothermia result is an important complication—Shivering, which is a complicated response of the body resulting in a pattern of muscular activity.

Aim: This study aims to compare the efficacy of I.v. hydrocortisone with I.v. low dose ketamine for prevention of shivering during spinal anesthesia.

Material & Methods: A Prospective Randomized trial with a sample size of 60 where patients allocated randomly using slot into 2 groups of Group-H (n=30) who received Inj. Hydrocortisone 2mg/kg and Group K (n=30) who received Inj. Ketamine 0.25mg/kg undergoes lower abdominal surgery under spinal anesthesia with 0.5% Bupivacaine of dosage 3ml. Parameters such as heart rate, blood pressure, oxygen saturation, temperature, were observed intraoperatively and postoperatively. The shivering grade, sedation score, patient requiring Inj. Pethidine as a rescue dose, motor, and sensory block was observed along with any side effects such as bradycardia, hypotension, or desaturation.

Result: In this study, there was no statistically significant difference (p>0.05) between the two drug groups in the grades of shivering. Clinically there were lower grades of shivering in the Hydrocortisone group when compared to the ketamine group at all timelines.

Conclusion: I.v. hydrocortisone 2mg/kg compared with the low dose I.v. ketamine 0.25mg/kg was clinically effective in reducing the incidence and intensity of shivering under spinal anesthesia on prophylactic use for lower abdominal surgery.

Keywords: shivering, ketamine, hydrocortisone, thermoregulation

Introduction

“The most effective system of cooling a man is to subjective him to anesthe...” as Pickering wrote in 1956 [1]. Hypothermia result is an important complication Shivering, which is a complicated response of the body resulting in a pattern of muscular activity. Due to thermoregulatory response to cold, shivering occurs following general or neuraxial anesthesia. Shivering causes severe physiological stress to the body. The most common treatment available for shivering includes both non-pharmacological and pharmacological methods. Non-pharmacological methods of treatment like external heating and pharmacological method include the number of drugs being studied like meperidine, tramadol, clonidine, dexmedetomidine, alfentanil, ketanserin, ketamine, magnesium sulphate, nefopam. Hydrocortisone etc.

To our knowledge, there is a limited study comparing hydrocortisone and ketamine as a prophylactic anti shivering agent. This prospective study was designed to study the comparative effect of Hydrocortisone and ketamine as a prophylactic agent for the prevention of shivering during spinal anesthesia in lower abdominal surgeries.

Aim of the study

The aim of this study is to compare the efficacy of I.v. hydrocortisone with I.v. Ketamine low dose of 0.25mg/kg in prevention of shivering during spinal anesthesia.
Objectives
Primary objective
To study the efficacy of ketamine and hydrocortisone in the prevention of intraoperative shivering.

Secondary objective
To assess the hemodynamic effect produced by both the drugs.
To study the side effects caused by the study of drugs.

Thermoregulation
Normal human core temperature ranges from 36.5 C to 37.5 C. Temperature sensation is acquired from the thermoreceptors present all over the body. Cold signal travel via Aδ nerve fibers, and Warm signal travel via unmyelinated C fibers [2]. But since C fibers also carry pain sensation, there is some degree of overlap. Hence intense heat may appear to intense pain. All the thermal signals travel via the spinothalamic tract. About 20% of the total thermal input to the central regulatory center is contributed by the hypothalamus, spinal cord, thoracic and abdominal tissues, and skin [3]. These thermal inputs they get integrated at the spinal cord prevent the significant and sense thermal signals which played important role in development of multilevel concept of thermal regulation.

The major response of the body to heat loss is by shivering and sweating which occur due to vasodilation and vasoconstriction. The principal defense against hypothermia in humans includes
1. Skin vasomotor activity.
2. Non-shivering thermogenesis.
3. Sweating.
4. Behavioral regulation.
5. Shivering.

Shivering is an oscillatory, involuntary muscular activity that increases the 600% of metabolic heat production above basal level. Shivering occurs when the preoptic region of the hypothalamus is cooled. The basic tremor frequency on the electromyogram is typically near 200 Hz.

Anaesthesia and Thermoregulation
Regional Anesthesia
During regional anesthesia the autonomic thermoregulation is impaired and result in hypothermia intraoperative. Neuraxial anesthesia both epidural and spinal reduces shivering threshold and vasoconstriction above the level of blockade indication alteration on the central control. The mechanism involved in the local anesthetic alters the afferent thermal inputs from the legs. Regional anesthesia alters the thermal input from the blocked region [4]. The patient on regional anesthesia does not perceive cold. Resulting in warmth with an autonomic response that is shivering [5]. Hence neuraxial anesthesia inhibits all thermoregulatory response. And also shivering and vasoconstriction threshold is decreased with behavioral regulation also impaired. All these conditions result in cold defenses triggering at a lower temperature than normal.

Ketamine
Ketamine is an aryl cyclohexylamine and congener of phencyclidine that produces “dissociative anesthesia” [6, 7]. Ketamine interact with multiple CNS receptors (N-methyl-d-aspartate [NMDA], opioid receptors, monoaminergic receptors, muscarinic receptors.

Anti-Shivering Effect: Ketamine, a competitive NMDA receptor antagonist, has anti shivering effect. It modulates thermoregulation at multiple sites. The NMDA receptor also modulate noradrenergic and serotonergic neurons in locus caeruleus.

Hydrocortisone
Hydrocortisone is a corticosteroid (CSs) belonging to classification of steroid hormones which are produced and secreted by the adrenal glands due to response by the pituitary adrenocorticotropic hormone, and it is regulated by hypothalamic corticotrophin releasing hormone.

Anti-shivering Effect: The exact mechanism by which cortisol prevents shivering is not known. A few clinical trials on animal studies show that cortisol have anabolic effect which increase the hepatic ATP level. Another animal study showed prolonged exposure of Cow to high temperature (8 weeks) caused depression in the level of cortisol depicting role of hydrocortisone in thermoregulatory mechanism.

Materials and Methods
This study on patients undergoing below umbilical surgeries under spinal anesthesia was approved by the Institutional ethical committee conducted by MMCHRI. This was a prospective randomized double-blind study on 60 patients over a period of 2 years.

After thorough preanesthetic assessment, with complete physical history, examination and investigation including complete blood count, renal function test, Serum Electrolytes, Serology and Blood glucose level, the study protocol was explained to each patient in the perioperative visit. After obtaining informed and written consent patient was taken up for surgery.

Sample Size and Randomisation: The size of the sample was calculated based on statistical data as 60. The patient was randomly divided into two groups (Group K n=30) received ketamine of dose 0.25mg/kg of body weight and another group (Group H n=30) received Inj Hydrocortisone 2mg/kg of body weight. Then 60 slots were prepared by the invigilator and randomly each number was allotted to one of the two group. A blind observer was allowed to choose the lot and the selected drug was being infused during the procedure.

A. Inclusion Criteria
i) Patient posted for elective lower abdominal and lower limb surgeries under spinal anesthesia.
ii) age-18-60 years
iii) Sex-male and female patient
iv) ASA-I-II

A. Exclusion Criteria
i) Patient refusal
ii) Patient with H/O convulsion, hypertension, coronary artery disease, thyroid dysfunction and diabetes mellitus.
iii) Patient on long term steroid therapy
iv) Patient allergy to the study drug and local anesthetics
v) Any contraindication to spinal anesthesia
vi) Patient initial body temperature by skin sensor monitor >100 F OR < 85 F
vii) Pregnancy and lactation
Procedure
Patients was shifted to operating theatre and monitors (Pulse oximetry, noninvasive arterial blood pressure monitor, electrocardiography and skin sensor temperature monitoring device) were connected and patient was cananized with 18G cannula and intravenous crystalloid fluid was given at rate of 10ml/kg body weight. The temperature in the operation theater was maintained at 22 degree Celsius and patient was covered with surgical drapes. IV fluids were used at the operation room temperature. Spinal anesthesia was performed under strict aseptic techniques with patient in sitting position, the parts was painted and draped. At L3-L4 space, 2ml of 2% lignocaine was used to infiltrated the skin. Then using 25G Quincke needle, subarachnoid space was punctured and 3ml of heavy bupivacaine 0.5% (15mg) was given after aspiration of clear and free flow CSF and patient was put in supine position. The study drug diluted in 10ml syringe with distilled water was given to the patient by the observer. Supplement oxygen with simple face mask at rate of 6lit/min was delivered. All parameters were monitored periodically. Surgery was started when adequate sensory blockade up to level T6 was achieved. At the end of the surgery the patient was shifted to the recovery room and monitored, covered with single layer of blanket and supplemented with Oxygen 4lit/min via face mask.

The following parameters was observed by the anesthesiologist
Patient characteristics and operation duration. Temperature-via skin sensor monitor before and after study drug administration and every 15 minutes until completion of the surgery. Other parameters that was monitored are-Heart rate, Systolic blood pressure, diastolic blood pressure, mean arterial pressure, saturation of oxygen, shivering grade periodically.

Shivering intensity was monitored by a grading system as described by wrench
Grade 0: No shivering, Grade 1: if one of the following are present such as Pilorection, peripheral cyanosis or vasoconstriction and, not visible muscle activity, Grade 2: Muscle activity which is visible and is confined to one group of muscle. Grade 3: Muscle activity which is confined to more than 1 group of muscle. Grade 4: Muscle activity which involves the whole body. If shivering grade > 3 was observed after spinal anesthesia with any of the study drug, then rescue drug Inj. Meperidine 25mg was given.

Statistical analysis
The data obtained was entered in Microsoft excel and analysed using Statistical package for Social Sciences (SPSS) version 16. The continuous variables such as heart rate, systolic blood pressure, etc., were summarized as mean and standard deviation while categorical variables such as demographic factors, grading of shivering and sedation, etc., were summarized as frequency and percentages. The data was depicted graphically in the form of Clustered bar charts and box and whisker plots. Chi-square test was used to test the statistical significance between the grades of shivering and sedation among the two drug groups. Independent t test was used to test the difference in heart rate; systolic, diastolic, mean arterial blood pressures and temperature between the two drug groups. Value of p of less than 0.05 has been considered significant.

Results

Table 1: Age and Gender distribution of the patients in the two drug groups (n=60)

| Variables        | Categories | Drug Group, n(%) | Total, n(%) |
|------------------|------------|------------------|-------------|
|                  |            | Ketamine         | Hydrocortisone |              |
| Age of the patient | <30 years | 2 (6.7%)        | 8 (26.7%)    | 10 (16.7%) |
|                  | 31-40 years | 4 (13.3%)       | 2 (6.7%)     | 6 (10.0%)  |
|                  | 41-50 years | 13 (43.3%)      | 11 (36.7%)   | 24 (40.0%) |
|                  | >50 years | 11 (36.7%)      | 9 (30.0%)    | 20 (33.3%) |
| Gender of the patient | Male | 13 (43.3%)      | 20 (66.7%)   | 33 (55.0%) |
|                  | Female | 17 (56.7%)      | 10 (33.3%)   | 27(45.0%)  |

Table 1 shows the distribution of age and gender of the patients in the two drug groups. Overall, majority of the patients (40%) belonged to the age group 41-50 years and more than half of them (55%) were males. Among the two drugs, the distribution of the age categories was similar except that there were more patients less than 30 years (26.7%) in the Hydrocortisone group. There were more males in Hydrocortisone group (66.7%). Figure 1 and Figure 2 shows the age and gender distribution graphically in the two drug groups.
Fig 1: Age wise graphical representation of the patients in the two drug group (n=60)

Table 2: Grading of shivering at various timelines (n=60)

| Timeline                        | Grade 0 | Grade 1 | Grade 2 | Grade 3 |
|---------------------------------|---------|---------|---------|---------|
| Shivering at the time of drug administration | 58 (96.7%) | 2 (3.3%) | 0       | 0       |
| Shivering at 1 min              | 53 (88.3%) | 2 (3.3%) | 5 (8.3%) | 0       |
| Shivering at 15 min             | 46 (76.7%) | 4 (6.7%) | 7 (11.7%) | 3 (5.0%)|
| Shivering at 30 min             | 30 (50.0%) | 11 (18.3%) | 10 (16.7%) | 9 (15.0%)|
| Shivering at 45 min             | 23 (38.3%) | 10 (16.7%) | 15 (25.0%) | 12 (20.0%)|
| Shivering at 60 min             | 26 (43.3%) | 9 (15.0%) | 22 (36.7%) | 3 (5.0%) |
| Shivering at 90 min             | 26 (43.3%) | 17 (28.3%) | 16 (26.7%) | 1 (1.7%) |

Fig 2: Graphical representation of shivering at various timelines among the patients (n=60)

Table 2 and figure 2 shows the distribution of the grades of shivering at various timelines among the patients. Most of the patients had grade 0 shivering at baseline, (96.7%), 1 minute (88.3%) and 15 minutes (76.7%). Similarly, nearly half of the patients had grade 0 shivering at 30 minutes (50%), 45 minutes (38.3%), 60 minutes (43.3%) and 90 minutes (43.3%).
**Table 3:** Temperature of the patient at various timelines (n=60)

| Temperature | Mean   | Standard Deviation |
|-------------|--------|--------------------|
| Baseline    | 88.01  | 11.57              |
| 1 minute    | 86.59  | 14.60              |
| 15 minutes  | 89.98  | 1.94               |
| 30 minutes  | 89.96  | 2.20               |
| 45 minutes  | 90.06  | 2.09               |
| 60 minutes  | 89.95  | 2.18               |
| 90 minutes  | 90.13  | 1.34               |

**Table 4:** Association of the grade of shivering with the two drug groups (n=60)

| Drug Group, n (%) | Ketamine | Hydrocortisone | Chi-square (p value)* |
|-------------------|----------|----------------|-----------------------|
| Shivering at the time of drug administration | Grade 0 | 28 (93.3%) | 30 (100.0%) | 2.069 (0.150) |
| Grade 1 | 2 (6.7%) | 0 | | |
| Shivering at 1 min | Grade 0 | 26 (86.7%) | 27 (90.0%) | 3.819 (0.148) |
| Grade 1 | 0 (0.0%) | 2 (6.7%) | | |
| Grade 2 | 4 (13.3%) | 1 (3.3%) | | |
| Grade 3 | 1 (3.3%) | 2 (6.7%) | | |
| Shivering at 15 min | Grade 0 | 23 (76.7%) | 23 (76.7%) | 2.619 (0.454) |
| Grade 1 | 1 (3.3%) | 3 (10.0%) | | |
| Grade 2 | 5 (16.7%) | 2 (6.7%) | | |
| Grade 3 | 1 (3.3%) | 2 (6.7%) | | |
| Shivering at 45 min | Grade 0 | 11 (36.7%) | 12 (40.0%) | 0.110 (0.991) |
| Grade 1 | 5 (16.7%) | 5 (16.7%) | | |
| Grade 2 | 8 (26.7%) | 7 (23.3%) | | |
| Grade 3 | 6 (20.0%) | 6 (20.0%) | | |
| Shivering at 60 min | Grade 0 | 12 (40.0%) | 14 (46.7%) | 1.487 (0.685) |
| Grade 1 | 6 (20.0%) | 3 (10.0%) | | |
| Grade 2 | 11 (36.7%) | 11 (36.7%) | | |
| Grade 3 | 1 (3.3%) | 2 (6.7%) | | |
| Shivering at 90 min | Grade 0 | 11 (36.7%) | 15 (50.0%) | 3.924 (0.270) |
| Grade 1 | 8 (26.7%) | 9 (30.0%) | | |
| Grade 2 | 11 (36.7%) | 5 (16.7%) | | |
| Grade 3 | 0 (0.0%) | 1 (3.3%) | | |

* p value by chi-square test

Table 4 shows the association between the grades of shivering in the two drug groups. There was no statistically significant difference (p>0.05) between the two drug groups in the grades of shivering. Clinically there were lower grades of shivering in the Hydrocortisone group when compared to the ketamine group at all timelines.

**Table 5:** Association of the heart rate at different timelines in the two drug groups (n=60)

| Heart rate at different timelines | Mean (±SD) | Drug Group | p value* |
|-----------------------------------|------------|------------|----------|
|                                    | Ketamine   | Hydrocortisone | |
| Baseline                           | 82.70 (±8.14) | 84.27 (±13.33) | 0.585 |
| 1 minute                           | 83.40 (±11.27) | 82.77 (±17.66) | 0.869 |
| 15 minutes                         | 81.33 (±8.90) | 76.20 (±12.89) | 0.078 |
| 30 minutes                         | 79.97 (±7.67) | 74.27 (±12.92) | 0.042 |
| 45 minutes                         | 78.90 (±8.96) | 73.67 (±12.95) | 0.074 |
| 60 minutes                         | 78.80 (±7.49) | 74.59 (±13.17) | 0.135 |
| 90 minutes                         | 77.25 (±7.63) | 78.62 (±11.03) | 0.629 |

*p value by Independent t test

Table 5 shows the association between the heart rates in the two drug groups. There was no statistically significant difference (p>0.05) between the two drug groups in terms of heart rate except at 30 minutes where patients in the Hydrocortisone had significantly (p=0.042) lower heart rate when compared to the ketamine group.

**Table 6:** Association of the Mean arterial blood pressure at different timelines in the two drug groups (n=60)

| Mean Arterial Blood Pressure | Drug Group | p value* |
|-------------------------------|------------|----------|
| Mean (±SD)                    | Ketamine   | Hydrocortisone | |
| Baseline                      | 92.77 (17.47) | 103.60 (15.46) | 0.014 |
| 1 minute                      | 93.40 (15.19) | 99.03 (12.87) | 0.127 |
| 15 minutes                    | 88.83 (10.29) | 91.70 (10.96) | 0.300 |
| 30 minutes                    | 88.93 (8.07) | 91.50 (8.97) | 0.249 |
| 45 minutes                    | 89.20 (8.70) | 91.83 (10.56) | 0.296 |
| 60 minutes                    | 89.63 (9.93) | 92.38 (12.21) | 0.347 |
| 90 minutes                    | 87.50 (9.22) | 92.95 (11.60) | 0.073 |

*p value by Independent t test
Table 6 shows the association between the mean arterial blood pressure in the two drug groups. There was no statistically significant difference (p>0.05) between the two drug groups in terms of mean arterial blood pressure except at baseline where patients in the Hydrocortisone had significantly (p=0.024) higher mean arterial blood pressure when compared to the ketamine group.

Table 7: Association of the temperature at different timelines in the two drug groups (n=60)

| Temperature [F] [Mean ±SD] | Drug Group | p value* |
|---------------------------|------------|---------|
|                           | Ketamine   | Hydrocortisone |
| Baseline                  | 87.24 (16.35) | 88.77 (1.91) | 0.611 |
| 1 minute                  | 87.03 (14.83) | 86.14 (14.58) | 0.816 |
| 15 minutes                | 90.25 (1.21) | 89.70 (2.46) | 0.280 |
| 30 minutes                | 90.16 (1.20) | 89.77 (2.88) | 0.489 |
| 45 minutes                | 89.95 (1.03) | 90.16 (2.78) | 0.695 |
| 60 minutes                | 90.06 (1.20) | 89.84 (2.89) | 0.708 |
| 90 minutes                | 89.99 (0.77) | 90.31 (1.83) | 0.447 |

*p value by Independent t test

Table 7 shows the association between the body temperature values in the two drug groups. There was no statistically significant difference (p>0.05) between the two drug groups in terms of the body temperature at all timelines.

Discussion

General and Regional anaesthesia both impede the thermoregulatory mechanism. All general anaesthetic drug can increase the threshold for sweating and decrease the shivering and vasoconstriction threshold. The body core temperature will decrease by 0.5 °C to 1.0 °C in regional or neuraxial anaesthesia. The incidence of shivering post anaesthesia is 5-65% or 40% respectively.

In the present study, both ketamine and hydrocortisone showed difference in reducing the incidence and intensity of shivering. There was were no statistically significant difference (p>0.05) between the two drug groups in the grades of shivering. But clinically there were lower grades of shivering in the Hydrocortisone group when compared to the ketamine group at all timelines. In a similar study conducted by Pawar et al. [9] which showed that Inj Hydrocortisone (1-2 mg kg1 iv) had effectiveness in prevention of shivering after knee arthroscopy under general anaesthesia. In other study, Qiao et al. [10] study showed the effectiveness of hydrocortisone 2 mg kg1 iv in treating post spinal anaesthesia in caesarean section. The mechanism by which hydrocortisone prevent shivering is unclear. It may be due to the alteration in thyroid hormone metabolism, anabolic effect or nitric oxide synthase activity.

In this study ketamine 0.25 mg/ kg is effective prophylactic drug in preventing shivering though there were no significance differences. This finding was found to agree with study conducted by Norouzi et al. compared two doses of ketamine 0.25 mg kg1 and 0.5 mg kg1 as good prophylactic in post anaesthesia shivering prevention. The above result was similar in another study surveyed by Dal et al. who found ketamine 0.5 mg kg1 iv which was compared as effective as meperidine 20 mg in post-operative shivering prevention after induction of general anaesthesia. Mechanism by which ketamine reduce shivering is by non-shivering thermogenesis action in the hypothalamus or by its action of beta-adrenergic action of nor epinephrine. All the hemodynamic parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, body temperature and oxygen saturation in our study was compared among both the drug group. There was no statistically significant difference (p>0.05) between the two drug groups in terms all the hemodynamic parameters at all timelines. This was found in agreeable with the study conducted by Shakya et al., Dal et al. and Sagir et al. [10]. found there were no hemodynamic changes with both the study group ketamine and hydrocortisone.

There is limitation in any study and in our study pertaining to showing the significant difference between both the study group in preventing shivering. Increase in the sample size or dosage of the both drugs may be needed to prove the significance and further studies on drug dosing in similar condition will be helpful in sorting this issue.

Conclusion

Shivering and all the consequences of shivering leads to various discomfort to the patient hence proper steps must be accompanied and taken to prevent shivering during intraoperative and postoperative period. The purpose of writing this article is to highlight the fact that there is still a lot to understand about the pathophysiology and management of post anaesthesia shivering, and thus more research is required in this subject. Hydrocortisone is more effective clinically as prophylactic in prevention of shivering under spinal anaesthesia. Hence, we conclude that i.v. hydrocortisone 2mg/kg on compared with low dose i.v. ketamine 0.25mg/kg was clinically effective in reducing the incidence and intensity of shivering under spinal anaesthesia on prophylactic use for lower abdominal surgery.

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