SciDoc Publishers
Infer, Interpret & Inspire Science

International Journal of Anesthesiology & Research (IJAR)
ISSN 2332-2780

Does the Administration of Preoperative Midazolam Assist in Maintaining Blood Glucose Norms in the Non - Diabetic Patient during the Perioperative Period?

Research Article

Tilak V[1*], Schoenberg C[2], Susan BG[3], Christina A[4]

[1] Assistant Professor, Rutgers, New Jersey Medical School, Newark, NJ, USA.
[2] Research Coordinator/Nurse Clinician, Rutgers, New Jersey Medical School, Newark, NJ, USA.
[3] Research Scientist, Cancer Research Program/NJSCR, Rutgers, The state University, USA.
[4] Medical Student, Rutgers, New Jersey Medical School (Current affiliation Columbia University, NY), USA.

Abstract

Introduction: Surgery induces stress response, which can cause elevated blood glucose level. In addition to tissue injury and inflammation, anxiety can contribute to the stress response. We measured the effect of preoperative midazolam administration on perioperative glucose levels to determine if midazolam administration will have beneficial effects on perioperative glucose levels.

Materials and Methods: Sixty non-diabetic patients between the ages of 18 and 80 were randomized into two groups. One group received preoperative midazolam and the other group received a placebo. The anesthetic regimen was controlled in both groups. Blood glucose levels were measures preoperatively and at predetermined intervals during surgery and in the post anesthesia care unit (PACU). The increases in the blood glucose levels from the preoperative value as well as percentage of patients with maximum glucose value less than 140mg/dl were compared between the groups.

Results: The patient characteristics and surgical as well as anesthetic factors were similar in both groups. There were no statistically significant differences in the percent increase in blood glucose levels between the groups. The median (interquartile range) percent increase from preoperative to maximum glucose in the midazolam group was 14.93(29.81) and in the placebo group was 24.98(27.11) with a P value of 0.56. The percentage of patients with blood glucose levels ≤ 140 was 86.67 in midazolam group vs 100 in the placebo group (P value .12).

Conclusion: Preoperative administration of midazolam did not cause attenuation of the hyperglycemic response compared to the placebo group.

Keywords: Blood Glucose; Midazolam; Anxiolysis; Perioperative; Stress Response.

Introduction

Blood glucose levels may be elevated in the perioperative period in response to stress [1-3]. Perioperative hyperglycemia is a risk factor for increased morbidity after surgery [4, 5]. The severity and the time period of hyperglycemia associated with harm have yet to be fully understood, however, it is likely that some degree of hyperglycemia may cause harm. When insulin/glucose homeostasis is challenged/stressed with oral glucose tolerance test a blood glucose value of >140mg/dl is considered as impaired glucose tolerance [6]. A recent consensus statement recommends that fasting blood glucose levels in non critically ill patients in hospital setting should be maintained at< 140mg/dl [7].

Stress can be induced by physical (injury, inflammation) as well as psychological (anxiety) factors. Preoperative anxiety has been shown to be associated with a hormonal stress response [8, 9]. It has been demonstrated that administration of midazolam preoperatively reduces anxiety [10]. A survey by Kain et al., [11] in 1997 revealed that approximately 75% of anesthesiologists routinely administer a sedative premedication to surgical patients. Currently, the majority of patients at our institution either do

***Corresponding Author**:
Vasanti Tilak, MD,
Assistant Professor, Department of Anesthesiology, UMDNJ, MSB E 538, 185 South Orange Avenue, Newark, NJ, 07103, USA.
Tel: 973-972-5254
Fax: 973-972-0582
E-mail: vasanti.tilak@rutgers.edu

Received: June 11, 2016
Accepted: July 14, 2016
Published: July 15, 2016

Citation: Tilak V, Schoenberg C, Susan BG, Christina A (2016) Does the Administration of Preoperative Midazolam Assist in Maintaining Blood Glucose Norms in the Non - Diabetic Patient during the Perioperative Period?. *Int J Anesth Res.* 4(7), 278-283. **doi:** http://dx.doi.org/10.19070/2332-2780-1600059

not receive anxiolytic premedication or receive it just before induction in the OR. The reason for this variation in practice may be due to the implementation of the time out procedure which is performed in the OR before the patient receives any medication. Several studies have looked at the impact of preoperative anxiety and premedication on outcomes such as stress response to laryngoscopy and intubation, intraoperative anesthetic requirements, postoperative nausea and vomiting and postoperative psychological and pain recovery [12-15].

We hypothesize that preoperative (in the holding area) midazolam will attenuate the neuroendocrine stress response by reducing psychological stress in the form of anxiety. This in turn may decrease the hyperglycemic response and help maintain perioperative blood glucose levels equal to or less than 140 mg/dl as this is the recommended value by ADA for hospital inpatients [7].

Materials and Methods

The study was registered at www.clinicaltrials.gov (NCT01641653). This prospective, single-blinded (subject only) randomized controlled trial was approved by the IRB of Rutgers New Jersey Medical School (formerly the University of Medicine and Dentistry of New Jersey). Patients scheduled to undergo inguinal or ventral hernia repair under general anesthesia were screened for potential enrollment into the study from June 2011 to August 2012. Patients were included into the study after providing informed consent. Criteria for enrollment included non-pregnant, English-speaking subjects between 18 and 80 years of age with no past medical history of diabetes, not currently taking steroid medication and with a fasting finger stick blood sugar less than 110 mg/dl, measured pre-operatively using the Abbott Freestyle™ portable monitoring device (Abbott Diabetic Care, Abbott Park, IL 60064). The glucose meters were calibrated according to the manufactures' recommendations.

Patients were randomized into two groups using a computer-generated randomization sheet on Microsoft Excel. One group received midazolam in the holding area and the other group received placebo. All anesthesia care providers were requested not to administer midazolam in the operating room. Ten minutes before entering the OR, study patients received either 1-2.5 mg IV midazolam or 2 cc of normal saline. All patients completed the State Trait Anxiety Inventory for Adults (STAI Form Y-1 and Y-2) pre-operatively to quantify the levels of current "state anxiety" and anxiety as a long-term personality trait, in order to determine a possible correlation with the subjects' perioperative glucose levels. Finger stick glucose levels were monitored once preoperatively, intraoperatively at 30-minute intervals following anesthetic induction, and twice in the Post-Anesthesia Care Unit (PACU), the first at 30 minutes post-arrival and the second at 60 minutes. The operations were performed by two surgeons to reduce the variability between surgical techniques.

Anesthetic protocol was as follows: All study participants were induced with 1.5-3 mg/kg propofol, 1-2 µg/kg fentanyl, and the muscle relaxant of choice. Maintenance medications included 1-1.5% Mac (end-tidal) of desflurane, 1.5-2 µg/kg/hr bolus of fentanyl, and the muscle relaxant of choice. Up to 1 µg/kg/hr of fentanyl was allowed if there was a 20% change in baseline blood pressure and/or heart rate intraoperatively. The anesthesia care team was allowed to choose the modality for postoperative pain control between intravenous Ketorolac, Morphine or TAP block if appropriate.

Data collected on each subject included age, gender, height, weight, body mass index (BMI), known family history of diabetes, marital status, current medications, menopausal status, durations of anesthesia and surgical times, preoperative and perioperative glucose levels, the time point of the maximum glucose level, quantity and type of fluid replacement, estimated blood loss, and amount, if any, of transfusion used. In addition, desflurane MAC and the Bispectral Index Score (BIS) were measured every 30 minutes post-induction. In the PACU, pain scores, using self reported visual analogue scale, 0 (no pain) to 10 (worst possible pain) were recorded at 30 and 60 minutes after arrival.

Data Analysis

Descriptive statistics were produced for all demographic, pre-op, intra-op, and post-op variables, allowing for the examination of data distributions, the characterizations of subjects relative to one another, and the ascertainment of data errors or outlier data points. Medians as well as means were calculated for variables whose frequency distributions were either skewed or contained outliers. Medians are presented for these variables, with both statistics being shown for maximum intra-op glucose.

Potential differences in demographic, pre-op, intra-op, and post-op characteristics by treatment group were assessed. Additionally, the following four measures were calculated and assessed for treatment group differences: percentage change from pre-op glucose to maximum glucose level, change from pre-op to maximum glucose level, time from incision to maximum glucose level, and percentage of subjects with intra-op glucose levels ≤ 140 mg/dl. The Wilcoxon rank-sum test or the *T*-test was used for continuous variables; the Pearson chi-square test was used for categorical variables. Both medians and means were calculated for the percentage change from pre-op to maximum glucose variable and the change from pre-op to maximum glucose variable as the frequency distributions were slightly skewed right. Additionally, p-values associated with both the *T*-test and the Wilcoxon rank-sum test were computed for these two variables. Spearman correlations were calculated to estimate the strength of the linear relationship between pain scores and PACU glucose levels.

All statistical tests were performed at the alpha=0.05 significance level. All statistical analyses were performed using SAS versions 9.2 or 9.4 (SAS Institute, Cary, North Carolina) on password-protected computers.

Results

Seventy three patients were consented for the study. One patients withdrew the consent and was removed. Twelve patients had finger stick glucose value > 110mg/dl and were excluded. Sixty patients completed the study, 30 in each group. We used a range of 1-2.5 mg rather than a fixed standard dose of 2 mg IV. One patient received 1 mg as the BMI was 18 and it was thought that 2mg may be excessive. One patient with a BMI of 44 received 2.5 mg. The rest of the patients in the study group received 2 mg

IV. There were no statistically significant differences between the two groups concerning patient demographics and intraoperative characteristics, as shown in Table 1. We measured the STAI scores preoperatively in all patients to determine anxiety levels. There were no differences in the anxiety levels between the two groups.

There was no statistically significant difference in intraoperative glucose levels and the PACU glucose levels between the two groups, as seen in Tables 2 and 3. 86.67% (26) of the patients in midazolam group had blood glucose levels ≤ than 140mg/dl vs. 100% (30) in the placebo group. The difference was not significant.

The median pre-op glucose levels were slightly lower in the placebo group though the difference was not statistically significant. The maximum intra-op glucose median and mean were 108/115 mg/dl for the midazolam group and 114/112 mg/dl for the placebo group. The percent increase from pre-op to maximum glucose level was lower in the midazolam group [Median 14.93(29.81), Mean 24.30(23.34)] compared to the placebo group [Median 24.98 (27.11), Mean 27.15(22.97)], though not significant. Time from incision to maximum glucose and induction to maximum glucose was longer but not significant in the midazolam group 43 vs 20 minutes and 60 vs 30 minutes respectively, as seen in Table 2. The pain scores and glucose levels in both groups in the PACU at 30 and 60 minutes were similar, as seen in Table 3.

Discussion

In this prospective, single-blinded (subject only) randomized trial we investigated the influence of preoperative midazolam administration on intra and postoperative glucose levels. We found no statistically significant difference in the intra-op or post-op glucose levels between the two groups. When comparing patients with perioperative blood glucose levels ≤ 140mg/dl there were no significant differences between the groups. Our hypothesis that the midazolam group will have significantly lower increase in the glucose level by reducing the psychological stress response was not validated.

Previous work suggests that the glucose levels increase during the perioperative period due to the metabolic and endocrine response

Table 1. Midazolam Study: Demographic and Intra-op Characteristics of Study Population by Randomized Group.

Characteristic	All Subjects (n=60)	Midazolam (n=30)	Placebo (n=30)	P-value
Age (years) (Mean (SD))	45.38 (13.05)	46.23 (12.96)	44.53 (13.32)	0.62
% Female (n)	35 (21)	43 (13)	27(8)	0.18
Ethnicity				0.60
% Black (n)	40 (24)	37 (11)	43 (13)	
% Hispanic (n)	42 (25)	40 (12)	43 (13)	
% White/Other (n)	18 (11)	23 (7)	13 (4)	
BMI (kg/m^2)	28.74 (5.71)	28.88 (5.17)	28.52 (6.02)	0.48
% Family Hx of Diabetes (n)	50 (30)	47 (14)	53 (16)	0.61
STAI Score Form 1	36.00 (14.50)	36.00 (13.00)	32.50 (17.00)	0.42
STAI Score Form 2	31.00 (17.00)	31.50 (15.00)	29.00 (19.00)	0.63
STAI Score (Mean of Forms 1 and 2)	34.00 (15.50)	35.25 (13.00)	32.00 (15.00)	0.42
Fentanyl Dose (mcg/kg)	2.18 (1.40)	2.15 (1.53)	2.23 (1.35)	0.55
Total IV Fluids (cc)	1000.00 (400.00)	1000.00 (200.00)	1000.00 (400.00)	0.36
Surgical Time (min)	73.50 (41.50)	73.00 (43.00)	72.50 (36.00)	0.83
Anesthesia Time (min)	117.50 (57.00)	112.00 (57.00)	125.00 (61.00)	0.88
Estimated Blood Loss (cc)				0.6
% < 30 cc (n)	43 (26)	47 (14)	40 (12)	
% ≥ 30 cc (n)	57 (34)	53 (16)	60 (18)	
% Antibiotics (n)	98 (59)	100 (30)	97 (29)	1.00
% Antibiotics with Glucose (n)	95 (56)	93 (28)	97 (28)	1.00
BIS Score (all times)	41.00 (15)	40.00 (15)	43.00 (14)	0.14
BIS Score (30 minutes post-induction)	43.00 (15)	40.50 (16)	44.50 (16)	0.21
BIS Score (60 minutes post-induction)	40.00 (13)	38.00 (11)	43.00 (13)	0.15
BIS Score (90 minutes post induction)	40.50 (14)	39.00 (10)	43.00 (16)	0.55
End-tidal (all times)	5.60 (1.83)	5.50 (1.70)	5.75 (1.85)	0.07
End-tidal (30 minutes post-induction)	5.63 (0.93)	5.33 (1.15)	5.80 (0.90)	0.09
End-tidal (60 minutes post-induction)	5.75 (1.75)	5.63 (2.25)	5.75 (1.55)	0.22
End-tidal (90 minutes post induction)	5.45 (3.15)	5.48 (2.70)	5.45 (3.20)	0.65

(All statistics are medians (interquartile range) unless otherwise indicated.)

Table 2. Midazolam Study: Intra-op Glucose-Related Measures by Randomized Group.

	All Subjects (n=60)	Midazolam (n=30)	Placebo (n=30)	P-value
Pre-op Glucose (mg/dL)	91.00 (16.50)	94.00 (12.00)	87.50 (18.00)	0.22
Intra-op Glucose (mg/dL) (all times)	103.00 (23.00)	101.00 (22.50)	105.00 (24.00)	0.44
Intra-op Glucose (mg/dL) (30 min post-induction)	105.00 (22.50)	100.50 (24.00)	106.00 (22.00)	0.64
Intra-op Glucose (mg/dL) (60 min post-induction)	102.00 (21.00)	102.50 (21.00)	101.00 (22.00)	0.69
Intra-op Glucose (mg/dL) (90 min post induction)	101.50 (21.00)	100.00 (25.00)	104.50 (18.00)	1.00
Intra-op Glucose (mg/dL) (120 min post induction)	104.00 (28.50)	104.00 (27.50)	109.00 (30.00)	0.37
% Increase Pre-op to Max Glucose	20.07 (28.49)	14.93 (29.81)	24.98 (27.11)	0.56
% Increase Pre-op to Max Glucose (Mean (SD))	25.73 (23.00)	24.30 (23.34)	27.15 (22.97)	0.64
Increase Pre-op to Max Glucose (mg/dL)	17.50 (23.50)	14.50 (25.00)	22.00 (23.00)	0.65
Increase Pre-op to Max Glucose (Mean (SD)) (mg/dL)	22.43 (19.66)	22.20 (22.18)	22.67 (17.16)	0.93
Maximum Intra-op Glucose (mg/dL)	111.50 (24.50)	108.00 (24.00)	114.00 (25.00)	0.87
Maximum Intra-op Glucose (mg/dL) (Mean (SD))	114.12 (19.95)	115.70 (23.90)	112.53 (15.27)	0.54
Median Intra-op Glucose Per Subject (mg/dL)	102.00 (19.00)	100.75 (22.50)	103.50 (19.00)	0.97
Time from Incision to Maximum Glucose (min)	40.00 (51.50)	43.50 (50.00)	20.00 (40.00)	0.16
Minutes post-induction at Maximum Glucose	60 (60)	60 (60)	30 (30)	0.11
% Intra-op Glucose Level ≤ 140 mg/dL (n)	93.33 (56)	86.67 (26)	100.00 (30)	0.12

All statistics are medians (interquartile range) unless otherwise indicated.)

Note: Case #61 has intra-op glucose reading times of 22 minutes and 60 minutes. The 22-minute reading was analyzed as a 30-minute reading.

Methods:

For p-values provided:

The Wilcoxon rank-sum test or the t-test assessed group differences in continuous variables. The Pearson chi-square test assessed group differences in categorical variables.

Table 3. Midazolam Study: Post-op Characteristics of Study Population by Randomized Group.

Characteristic	All Subjects (n=60)	Midazolam (n=30)	Placebo (n=30)	P-value/CI Overlap
PACU 30-minute Pain Score	6.00 (5.00)	6.00 (6.00)	6.00 (6.00)	0.51
PACU 60-minute Pain Score	5.00 (4.50)	5.00 (5.00)	5.00 (4.00)	0.40
PACU Pain Score (mean of 30-and 60-minute scores)	5.50 (5.00)	5.25 (5.00)	6.00 (4.00)	0.45
PACU 30-minute Glucose (mg/dL)	99.50 (23.00)	101.50 (19.00)	96.50 (26.00)	0.62
PACU 60-minute Glucose (mg/dL)	101.00 (26.00)	101.50 (28.00)	96.00 (24.00)	0.78
PACU Glucose (mg/dL) (mean of 30- and 60-minute values)	100.00 (26.00)	101.25 (27.50)	96.00 (30.50)	0.67
Spearman Correlation (95% CI) between 30-Minute Pain Scores and 30-Minute PACU Glucose	r=0.04 (-0.21,0.30) p=0.74	r=0.08 (-0.29,0.43) p=0.66	r=-0.01 (-0.37,0.35) p=0.94	Not significant (CI overlap)
Spearman Correlation (95% CI) between 60-Minute Pain Scores and 60-Minute PACU Glucose	r=0.06 (-0.20,0.31) p=0.66	r=0.19 (-0.19,0.51) p=0.33	r=-0.06 (-0.41,0.31) p=0.75	Not significant (CI overlap)
Spearman Correlation (95% CI) between Mean Pain Scores and Mean PACU Glucose	r=0.04 (-0.21,0.29) p=0.74	r=0.10 (-0.27,0.49) p=0.58	r=-0.06 (-0.41,0.31) p=0.75	Not significant (CI overlap)

to stress [2, 16]. Our study demonstrated an overall small increase in glucose levels in non-diabetic patients undergoing a low risk procedure (20% overall, 15% midazolam group, 25% placebo group). Abdelmalak et al., [17] have reported an increase in glucose levels of 72 ± 45 mg/dl in non-diabetic patients undergoing major non-cardiac surgery. In our group the increase was much smaller (22 ± 19). This may be due to the fact that the surgical procedure involved was hernia repair, which is considered a low risk procedure according to the modified Johns Hopkins surgical criteria.

The association between perioperative hyperglycemia and increased morbidity has been extensively studied and described in the literature [4, 5, 18]. There is no consensus on the cut off for acceptable glucose levels though there is a general agreement about the necessity to avoid hyperglycemia in the perioperative period. Numerous investigators have compared various anesthetic techniques that can modify the neuroendocrine and/or the hyperglycemic response. Regional anesthesia has been shown to be superior to inhalation technique to decrease the hyperglycemic response [19, 20] and a combination of propofol and opioids has been demonstrated to suppress the endocrine and metabolic response to surgical stress [21, 22]. Dawson et al., [23] compared induction with midazolam and thiopentone in female patients for pelvic surgery and found no differences in glycemic or adrenocortical response. Ekbom et al., [24] studied the effects of midazolam and nitrous oxide on glucose and cortisol levels when administered for sedation before intravenous access in children. After midazolam the cortisol levels were significantly lower than those after nitrous oxide. Furthermore the levels were lower than those in the unstressed children. It was postulated that the results were not due to the superiority of midazolam to reduce anxiety associated with intravenous access but due to its pharmacological effects on stress hormones. Heine et al., [25] described the effects of premedication with midazolam on immunological and cardiovascular stress in patients receiving retrobulbar block by measuring leukocyte subpopulation and cardiovascular parameters. Midazolam was found to attenuate both responses.

This study was not designed to observe complications from elevated glucose levels between the groups. It was conducted to determine if administration of preoperative medication will reduce the hyperglycemic response.

Preoperative sedative medication is administered to achieve one or more of the following: sedation, amnesia, anxiolysis, pain control, decreased intraoperative anesthetic requirements and prevention of postoperative nausea and vomiting [12, 13, 26]. Kain et al., [13] described better psychological and pain recovery in patients receiving midazolam premedication before outpatient surgery under general anesthesia. However, the study did not measure the stress hormone levels and could not comment on the mechanism of post operative effects of midazolam.

We chose to measure perioperative glucose levels which are a marker of metabolic response to surgical stress. Besides demographic characteristics we compared data on variables that would contribute to the level of stress in the perioperative period. Preoperatively we recorded the level of anxiety. Chronic anxiety is a predictor of both pre and post operative mood and fear as demonstrated by Johnson et al., [27] All our patients completed the State Trait Anxiety Inventory for Adults (STAI Form Y-1 and Y-2) pre-operatively to compare the current "state of anxiety" and anxiety as a long-term personality trait. There were no significant differences in the scores in the two groups indication that the level of anxiety in both groups was similar. Intraoperative dose of fentanyl, end tidal inhalation agent concentration and BIS values were recorded in both groups to compare the level/depth of anesthesia. Duration of surgery was recorded as Tan et al., [28] have shown it to be a predictor for hyperglycemia. We also collected information on antibiotic administration since many times antibiotics are mixed in glucose containing solutions. Amount of blood loss, which could modify stress response, was also recorded [29]. In the PACU we recorded pain scores as pain can enhance stress response. There were no differences between the groups regarding these variable.

The reason for the lack of difference between the groups in our study may be that the midazolam was given only 10 minutes before entering the operating room. The anxiety and the resulting stress may need to be blocked earlier, potentially the day before surgery. The dose of midazolam given was 1-2.5 mg IV rather than a mg/kg dose. The dose may not have been sufficient to achieve significant reduction in anxiety. The level of anxiolysis and sedation after the administration of the drug/placebo was not documented. This may also have caused variability in the level of stress reduction achieved. We did however find that the percent increase in glucose levels was lower in the midazolam group and the time to maximum glucose levels post induction and post incision were longer in the midazolam group. This may indicate some beneficial effects of the anxiolysis from midazolam earlier in the case.

Our results, in context of previous work, suggest that it is important to find techniques to control perioperative glucose levels. The doses and timing of midazolam used in our protocol were not sufficient to yield statistically significant differences in glucose levels. While previous literature has demonstrated some benefit to anxiolysis prior to surgery, our results suggest that standard doses of midazolam are not sufficient to improve intra-op blood glucose levels. More studies are needed to find the best protocol to attenuate the hyperglycemic response in the perioperative period.

References

[1]. Weissman C (1990) The metabolic response to stress: an overview and update. Anesthesiology 73(2): 308-327.

[2]. Halter JB, Pflug AE, Porte D (1997) Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 45(5): 936-944.

[3]. Derbyshire DR, Smith G (1984) Sympathoadrenal responses to anaesthesia and surgery. British Journal of Anesthesia 56(7): 725-739.

[4]. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, et al. (2010) Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 33(8): 1783-1788.

[5]. Kwon S, Thompson R, Dellinger P, Yanez D, Farrohki R, et al. (2013) Importance of perioperative glycemic control in general surgery: a report from the surgical care and outcomes assessment program. Ann Surg 257(1): 8–14.

[6]. American Diabetes Association (2015) Classification and diagnosis of diabetes. Diabetes Care 38(1): S8–S16.

[7]. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, et al. (2009) American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 32(6): 1119–1131.

[8]. Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS (1993) Exposure to physical; and psychological stressors elevates plasma interleukin 6: relationship to the activation of the hypothalamic-pituitary-adrenal axis. Endo-

crinology 133(6): 2523-2530.
[9]. Price DB, Thaler M, Mason JW. (1957) Preoperative emotional states and adrenal cortical activity; studies on cardiac and pulmonary surgery patients. AMA Arch Neurol Psychiatry 77(6): 646-656.
[10]. Reves G, Glass P, Lubarsky D (2000) Nonbarbiturate intravenous anesthetics; Anesthesia (5th Edn), Churchill Livingstone, Philadelphia. 228-272.
[11]. Kain ZN1, Mayes LC, Bell C, Weisman S, Hofstadter MB et al.,(1997) Premedication in the United States: A status report. Anesth Analg 84(2): 427-432.
[12]. Maranets I, Kain ZN (1999) Preoperative anxiety and intraoperative anesthetic requirements. Anesth Analg 89(6): 1346–1351.
[13]. Kain ZN, Sevarino F, Pincus S, Alexander GM, Wang SM, et al (2000). Attenuation of the preoperative stress response with midazolam: effects on postoperative outcomes. Anesthesiology 93(1): 141-147.
[14]. Bergendahl HT, Eksborg S, Kogner P, Lonngvist PA (1999) Neuropeptide Y response to tracheal intubation in anaesthetized children: effects of clonidine vs midazolam as premedication. Br J Anaesth 82(3): 391-394.
[15]. Das A, Saha TK, Majumdar S, Mandal RD, Mukherjee A, et al. (2013) Comparative evaluation of oral clonidine and midazolam as premedication on preoperative sedation and laryngoscopic stress response attenuation for the patients undergoing general anaesthesia. Int J Med Public Health 3(3): 200-206.
[16]. Bower WF, Lee PY, Kong AP, Jiang JY, Underwood MJ, et al. (2010) Perioperative hyperglycemia: a consideration for general surgery? Am J Surg 199(2): 240–248.
[17]. Abdelmalak BB, Bonilla AM, Yang D, Chowdary HT, Gottlieb A, et al., (2013) The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. Anesth Analg 116(5): 1116-1122.
[18]. Richards JE, Kauffmann RM, Obremskey WT, May AK (2013) Stress-induced hyperglycemia as a risk factor for surgical-site infection in non-diabetic orthopaedic trauma patients admitted to the intensive care unit. J Orthop Trauma 27(1): 16-21.
[19]. Lattermann R, Schricker T, Wachter U, Georgieff M, Goertz A (2001) Understanding the mechanisms by which isoflurane modifies the hyperglycemic response to surgery. Anesth Analg 93(1): 121-127.
[20]. Gottschalk A, Rink B, Smektala R, Piontek A, Ellger B, et al. (2014) Spinal anesthesia protects against perioperative hyperglycemia in patients undergoing hip arthroplasty. Journal of Clinical Anesthesia 26(6): 455-460.
[21]. Schricker T, Carli F, Schreiber M, Wachter U, Geisser W, et al. (2000) Propofol/sufentanil anesthesia suppresses the metabolic and endocrine response during, not after, lower abdominal surgery. Anesth Analg 90(2): 450-455.
[22]. Azemati S, Savai M, Khosravi MB, Allhyari E, Jahanmiri F, et al. (2013) Combination of remifentanyl with isoflurane or propofol: effects on the surgical stress response. Acta Anaesthesiol Belg 64(1): 25-31.
[23]. Dawson D, Sear JW (1986) Influence of induction of anaesthesia with midazolam on the neuro-endocrine response to surgery. Anaesthesia 41(3): 268-271.
[24]. Ekbom K, Kalman S, Jakobsson J, Marcus C (2012) Effects of midazolam and nitrous Oxide on endocrine and metabolic measurements in children. Horm Res Paediatr 77(5): 309-319.
[25]. Heine GH, Weindler J, Gabriel HH, Kindermann W, Ruprecht KW (2003) Oral premedication with low dose midazolam modifies the immunological stress reaction after the setting of retrobulbar anaesthesia. Br J Ophthalmol 87: 1020–1024.
[26]. Wang S, Kain ZN (2000) Preoperative anxiety and postoperative nausea and vomiting in children: Is there an association? Anesth Analg 90(3): 571-575.
[27]. Johnson JE, Dabbs JM, Leventhal H (1970) Psychosocial factors in the welfare of surgical patients. Nurs Res 19(1): 18-29.
[28]. Tan BL, Lim TA (2006) Factors influencing post-operative hyperglycaemia in type 2 diabetes mellitus patients managed without intra-operative insulin. Med J Malaysia 61(1): 122-124.
[29]. Thorell A, Nygren J, Ljungqvist O (1999) Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care 2(1): 69-78.