ORIGINAL ARTICLE

A Comparative Study of the Tolerance to Stress Response Under Spinal Anaesthesia in Diabetic Versus Non-Diabetic Patients

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ABSTRACT

Introduction: Activation of sympathetic nervous system, increase of catabolic hormone release and pituitary gland suppression are responses to surgical stress. Neural blockade via epidural or spinal anesthesia, intravenous administration of high-dose of strong opioid analgesics, and infusion of anabolic hormones such as insulin are three main methods for balancing stress responses to surgery. However, there are conflicting reports about the extent of autonomic disturbances occurring after inducing spinal anesthesia in diabetic patients due to underlying autonomic neuropathy. Methodology: An observational cohort study was conducted in an operative room of a tertiary health care center involving 25 diabetic patients and 25 non-diabetic patients to evaluate the tolerance to stress. The diabetic patients undergone an exercise tolerance test to evaluate for postural hypotension which would indicate presence of autonomic neuropathy. Stress parameters such as heart rate, mean blood pressure, blood glucose level, and temperature were measured at regular intervals pre, peri- and post-operatively. Results: Intraoperative heart rate, mean blood pressure, and blood glucose level were high in diabetic patients with autonomic neuropathy ($p \leq 0.05$). Temperature was higher in diabetic patients with autonomic neuropathy initially ($p \leq 0.05$) and had a higher fall peri-and post-operatively (T=15 minutes, T=20 minutes, and T=after surgery). A significant differences in the parameters of stress response were observed in diabetic patients with autonomic neuropathy. Conclusion: By understanding the correlation between stress-response in diabetic patients with autonomic neuropathy peri-operatively will help the anesthetist to provide customized services to every patient.

Keywords
Diabetic, Non-diabetic, Autonomic Neuropathy, Spinal Anesthesia, Stress Response.

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INTRODUCTION

Prevalence of diabetes mellitus has been steadily rising throughout the world for the past 20–30 years in both adults and children.[1] Inevitably, there will be an enormous burden on anesthetic services in diabetic patients requiring surgery regarding their disease.

Anesthesia and surgery induce physiological responses such as fluctuations in the endocrine system (such as increase in cortisol, adrenaline, noradrenaline) and psychological strain (distress and fear). This causes secretion of hormones such as catecholamines, cortisol, glucagon, and growth hormone leading to an increment in plasma proteins, sodium retention, potassium loss, and an increase in blood sugar levels.

Moreover, surgical stress also stimulates sympathetic activity thereby increasing nor-adrenaline levels which result in decreased insulin secretion and glucose consumption. This causes an increase in gluconeogenesis, invariably resulting in hyperglycaemia,[2] further leading to an increase in chances of postoperative infections and mortality due to weakness in the immune system. Besides, these hemodynamic changes lead to cardiovascular, neural, and renal damage.[3]

The stress response gets minimized when local anesthetics are used via epidural or intrathecal, notably in lower abdominal operations. Preoperative use of appropriate fluid and glucose reduces unconscionable catabolism.

However, there are conflicting reports about the extent of autonomic disturbances that occur after inducing spinal anesthesia in diabetic patients which may occur due to underlying autonomic neuropathy in some patients. The present research focuses on evaluating and comparing the vitals of diabetic versus non-diabetic patients under spinal anesthesia and possibly overcoming the gaps in the existing knowledge of autonomic disturbances in diabetic patients. It also attempts to establish a correlation between autonomic neuropathy, and its impact on autonomic disturbances in diabetic patients.

MATERIALS AND METHOD

Institutional Ethical Committee clearance was obtained before the study was commenced.

Type of Study: Observational Study.

Study Design: Cohort Study.

Setting: An Operative room of a Tertiary Health Care centre.

Inclusion criteria: 25 diabetic and 25 non-diabetic patients undergoing lower abdominal surgery from age group of 18–60 years. Patients were grouped according to ASA (American Society of Anesthesiologist) classification.[4] Patients with ASA I and II were taken for this study. The diabetic patients were put under exercise tolerance test[5] and were checked for postural hypotension[6] to find out the presence of autonomic neuropathy.[7]

Exclusion criteria: Pediatric and geriatric age groups were excluded from the study. Patients with cardiovascular diseases, history of excessive drugs and alcohol intake, previous history of anxiety or stress were excluded.

Data Collection Method: On an average our department receives 12-14 diabetic patients per month fitting into inclusion criteria of the research. Considering this as the baseline data of patient inflow, the study period (2 months) included 25 diabetic patients in the survey. An equal number of non-diabetic patients were included. Therefore, this was a cohort comparative study with a total sample size of 50 patients. The required data were collected from the patients which were then tabulated and compared. Written informed consent of the patient was taken and the whole procedure was explained to them in their vernacular language.

Procedure: In this study, the patients did not receive any anti-anxiety medication before entering the operating room, and patients were put NPO (nil per os) for 8 hours before surgery. Preoperative Blood HbA1c was measured to identify patients with undiagnosed diabetes. The diabetic patients were further divided into patients with autonomic neuropathy and patients without having autonomic neuropathy and the subsequent data was collected accordingly. Both groups of patients received 0.5% Bupivacaine (heavy) 3 ml using a 25gauge spinal needle at L4-L5 level.

Assurance of neuraxial blockade (the sensory blockade was checked by pin-prick method and motor blockade was checked by Bromage scale[8,9]) is done. Score 1 indicated that anesthesia was successful, and the patient was ready to undergo the surgical procedure. The hemodynamic parameters which included heart rate, and blood pressure, were monitored. Also, temperature changes and variation in blood sugar levels were monitored continuously. Different parameters were checked at different intervals.

Bedside blood glucose level was measured in all patients using a glucometer in the index finger of the right hand maintaining the sterility conditions-

- 10 minutes before anesthesia.
- 20 minutes and 60 minutes after initiation of anesthesia.
- Immediately after the surgical procedure is over.

Standard monitoring was used including non-invasive blood pressure (NIBP) monitoring, and 3 lead electrocardiogram monitoring. A temperature probe was attached to the axilla of the patient and the variations in temperature were measured. Heart rate, mean arterial pressure, and temperature were measured-

- Promptly before anesthesia.
- For every 5 minutes for the first 30 minutes after inducing the patient with spinal anesthesia.
- For every 15 minutes after the first 30 minutes until the surgical procedure is over.
- Immediately after surgery.

The appropriate data was collected and then evaluated. The variation of stress response in diabetic patients with and without autonomic neuropathy was measured and then compared with the stress response in non-diabetic patients. The data obtained was then put under statistical analysis and the degree to which diabetic patients were prone to detrimental effects of stress response was ascertained.

Statistical Analysis: The data obtained was entered in Microsoft Excel and analyzed using statistical software such as Primer of Biostatistics and EpiInfo.[7] Quantitative data were presented in the form of mean and standard deviation. Qualitative data were presented in the form of numbers and percentages. Statistical tests of significance such as t-test and repeated measures ANOVA was applied and then p-value was calculated to check for statistically significant data.

RESULTS

Within the stipulated time of the current study, the hospital where this study was conducted, received 22 diabetic patients and 25 non-diabetic patients who were posted for surgery under spinal anesthesia and who met the requirements of the current study. 47 patients (22 diabetics and 25 non-diabetics) between the age of 18 and 60 were studied. The diabetic patients were further divided into patients with autonomic neuropathy and patients without autonomic neuropathy by checking for orthostatic hypotension and putting them under exercise tolerance test preoperatively. Among the diabetics, 6 patients were found to have diabetic autonomic neuropathy. There were 14 Females and 33 Males.

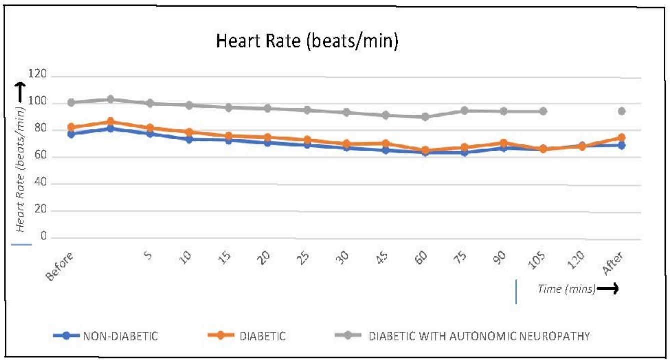

Figure 1: Changes in Heart Rate (beats/min) of Non-Diabetic patients, Diabetic patients and Diabetic Patients with Autonomic Neuropathy (AN).

Table I: Changes in Heart Rate (beats/min) of non-Diabetic patients, Diabetic patients, and Diabetic Patients with Autonomic Neuropathy (AN) and their level of significance

Time (Mins)		Heart Rate (beats/min) Non-Diabetic (Mean±SD)	Diabetic (Mean±SD)	Diabetic with AN (Mean±SD)	p-value Non-Diabetic vs Diabetic	Non-Diabetic vs Diabetic with AN
Before induction		77.32±9.66	82±10	100.67±5.12	0.144	<0.001
At induction		81.32±10.85	86.56±9.06	103±5.07	0.117	<0.001
After induction	5	77.40±10.19	81.81±8.99	100.17±5.46	0.165	<0.001
	10	73.40±9.71	78.69±8.62	98.5±5.71	0.084	<0.001
	15	72.64±9.81	75.81±9.38	96.83±5.81	0.311	<0.001
	20	70.68±10.55	74.88±8.30	96.17±5.49	0.202	<0.001
After Surgery		68.8±9.5	74.5±9.11	94.17±5.34	0.064	<0.001

The heart rate at various intervals for the 47 patients was evaluated.

Referring to Figure 1, it is seen that the heart rate was higher in diabetic patients with autonomic neuropathy and showed little variation over time. On the other hand, non-diabetic patients and diabetic patients without autonomic neuropathy showed comparable values of heart rate with higher variation over time than that of patients with autonomic neuropathy. All three groups showed an increase in heart rate at the time of induction.

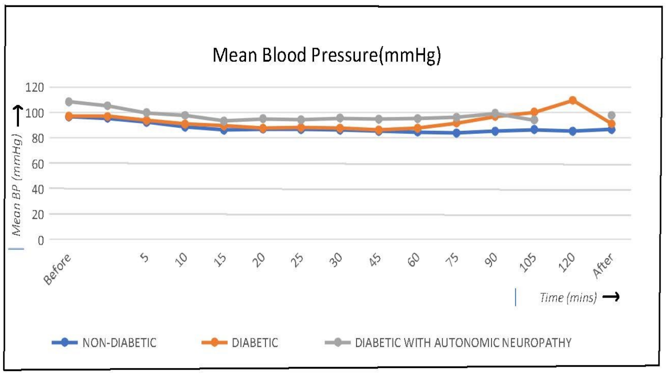

Figure 2 : Changes in Mean Blood Pressure (BP)(mmHg) of Non-Diabetic patients, Diabetic patients, and Diabetic Patients with Autonomic Neuropathy (AN).

Furthermore, referring to Table I, it is seen that difference in heart rate between diabetic patients with autonomic neuropathy and non-diabetic patients was statistically significant ($p \leq 0.05$) for all time intervals. Contrarily, the difference in heart rate between diabetic patients and non-diabetic patients was statistically insignificant ($p > 0.05$). Thus, this shows that heart rate was higher in diabetic patients with autonomic neuropathy throughout.

The Mean Blood Pressure at various intervals for the 47 patients was evaluated.

Referring to Figure 2, it is seen that the mean blood pressure was higher in diabetic patients with autonomic neuropathy. On the other hand, non-diabetic patients and diabetic patients without autonomic neuropathy showed comparable values of mean blood pressure.

Furthermore, referring to Table 2, it is seen that difference in mean BP between diabetic patients with autonomic neuropathy and non-diabetic patients was statistically significant ($p \leq 0.05$) for all time intervals (except at T=15minutes). Contrarily, the difference in mean BP between diabetic patients and non-diabetic patients was statistically insignificant ($p > 0.05$).

The Blood Sugar Level (BSL) at various intervals for the 47 patients was evaluated.

Referring to Figure 3, it is seen that the BSL was higher in diabetic patients and diabetic patients with autonomic neuropathy. On the other hand, non-diabetic patients showed comparable values of BSL.

Table II : Changes in Mean Blood Pressure (BP)(mmHg) of Non-Diabetic patients, Diabetic patients and Diabetic Patients with Autonomic Neuropathy (AN) and their level of significance.

Time (mins)		Mean Blood Pressure (mmHg)			p-value	
		Non-Diabetic (Mean±SD)	Diabetic (Mean±SD)	Diabetic with AN (Mean±SD)	Non-Diabetic vs Diabetic	Non-Diabetic vs Diabetic with AN
Before induction		96.47±7.63	97.06±6.15	108.28±5.59	0.795	0.001
At induction		95.41±8.67	96.85±7.35	105.11±6.6	0.583	0.016
After induction	5	92.24±8.01	93.81±8.02	99.78±6.61	0.543	0.042
	10	88.57±7.84	90.79±5.98	97.67±7.46	0.337	0.015
	15	86.17±7.45	89.52±5.41	93.17±8.86	0.12	0.054
	20	86.72±7.13	87.38±5.09	94.83±7.5	0.748	0.019
After Surgery		86.6±5.3	90.94±7.12	97.67±6.42	0.031	<0.001

Table III : Changes in Blood Sugar Level (BSL)(mg/dL) of Non-Diabetic patients, Diabetic patients and Diabetic Patients with Autonomic Neuropathy (AN) and their level of significance.

Time (mins)	Blood Sugar Level (mg/dL)			p-value	
	Non-Diabetic (Mean±SD)	Diabetic (Mean± SD)	Diabetic with AN (Mean± SD)	Non-Diabetic vs Diabetic	Non-Diabetic vs Diabetic with AN
Before induction	89±13.42	114.31±37.62	165.67±16.99	0.004	<0.001
After induction (at 20 mins)	87.32±13.65	109.19±32.05	150.33±22.84	0.004	<0.001
After Surgery	86.24±14.79	108.38±32.95	138.5±20.89	0.005	<0.001

Furthermore, referring to Table 3, it is seen that difference in BSL between diabetic patients with autonomic neuropathy and non-diabetic patients was statistically significant ($p \leq 0.05$) for all time intervals. Also, the difference in BSL between diabetic patients and non-diabetic patients was statistically significant ($p \leq 0.05$) for all time intervals.

Table IV : Changes in Temperature (degree Celsius) of Non-Diabetic patients, Diabetic patients, and Diabetic Patients with Autonomic Neuropathy (AN) and their level of significance.

Time (mins)	Temperature (degree Celsius)			p-value	
	Non-Diabetic (Mean±SD)	Diabetic (Mean±SD)	Diabetic with AN (Mean± SD)	Non-Diabetic vs Diabetic	Non-Diabetic vs Diabetic with AN
Before induction	36.95±0.08	37.04±0.08	37.13±0.05	0.001	<0.001
At induction	36.96±0.07	37.04±0.08	37.13±0.05	0.002	<0.001
After induction 5	36.91±0.10	37.01±0.1	37.03±0.09	0.003	0.012
10	36.88±0.12	36.94±0.11	37.00±0.10	0.115	0.032
15	36.82±0.17	36.89±0.15	36.80±0.11	0.187	0.787
20	36.76±0.15	36.84±0.13	36.71±0.12	0.088	0.460
After Surgery	36.44±0.48	36.48±0.29	36.65±0.24	0.766	0.311

DISCUSSION

Diabetes mellitus (DM) is a ubiquitous disease found in all parts of the world. DM increases the risk of cardiovascular diseases, nephropathies, retinopathies, perioperative hypotension, and intra-operative morbidity. Hyperglycaemia in DM is associated with microvascular and macrovascular complications.[10]

Long-term uncontrolled diabetes leads to autonomic nervous dysfunction. Autonomic neuropathy causes severe sympathetic and parasympathetic dysregulation resulting in various complications.[11] The pathogenesis of autonomic neuropathy is complex and involves numerous

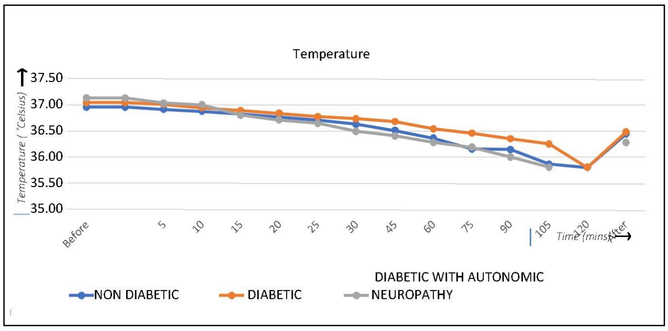

Figure 4 : Changes in Temperature (degree Celsius) of Non-Diabetic patients, Diabetic patients, and Diabetic Patients with Autonomic Neuropathy (AN).

pathways upregulated or downregulated due to hyperglycaemia resulting in nervous ischaemia and cellular death. Thus, these complications present a major challenge to the anesthetist. Autonomic neuropathy may remain subclinical for several years until the patient presents with exercise intolerance, postural hypotension, nephropathy, and cardiac myopathy.

Heart Rate:

Changes in heart rate (HR) that is determined by the balance between sympathetic and parasympathetic tones and can help in detecting autonomic neuropathy before the disease becomes symptomatic. All three groups showed an increase in HR at the time of induction which might be caused due to the pain and fear at the time of induction causing sympathetic stimulation.

According to the current study, the heart rate was increased in diabetic patients with autonomic neuropathy throughout. The difference in heart rate in diabetic patients without autonomic neuropathy and non-diabetic patients was statistically insignificant. Also, the variation in heart rate overtime was less than that of diabetic patients without autonomic neuropathy and non-diabetic patients.

The results of the current study correlate with the article published by Dimitropoulos G *et al.* (2014)[12] who stated that Diabetic Autonomic Neuropathy (DAN) is accompanied by a reduction in parasympathetic tone resulting in increased sympathetic activity. He also stated that fixed heart rate which does not change during sleep, exercise or stress is a sign of complete cardiac denervation occurring in DAN[13] which corresponds to the current study.

Vinayagam S *et al.* (2019) demonstrated that patients with DM with attenuated parasympathetic tones (probably due to underlying DAN) had lower heart rate variability[14] which corresponds to the current study.

Therefore, the result of the current study concludes that spinal anesthesia did not affect DM patients having DAN since their autonomic nervous function (sympathetic-parasympathetic regulation) was already decreased and they had little change in HR and PR over time perioperatively. Based on the observation that HR and PR changed comparably over time, the results of the present study confirmed that spinal anesthesia affected the autonomic nervous function in DM patients without DAN and non-diabetic (ND) patients.

Blood Pressure:

According to the current study, systolic blood pressure (SBP) and mean blood pressure (MBP) were increased in DM patients with DAN throughout with little change over time. The difference in SBP and MBP in diabetic patients without autonomic neuropathy and non-diabetic patients was statistically insignificant. In contrast, diastolic blood pressure (DBP) of the three groups remain comparable over time.

The results of the current study correlates with the study performed by Lee S. (2015)[15] in which the SBP and MBP were significantly higher in uncontrolled DM groups.

Yokoyama H et al. (2007) in his study concluded that increased arterial stiffness caused by vascular dysfunction in DM leads to an increase in systolic BP.[16]

Thus, the result of the current study concludes that a high SBP in DM can be due to the effects of increased blood sugar on the vascular endothelium and peripheral nerves and its interaction with various vascular and metabolic factors[17] resulting in arterial stiffness and loss of compliance. The high SBP and MBP could both reflect arterial stiffness secondary to neuropathy and associated vascular damage.

The current study, however, does not take into consideration the extent of autonomic neuropathy in the patients. Further studies could be conducted emphasizing on evaluating the extent of autonomic neuropathy and its impact on hemodynamic parameters in patients under spinal anesthesia.

Blood Sugar Level:

According to the current study, blood sugar levels remain comparable to the baseline perioperatively in all three groups namely ND patients, DM patients without DAN, and patients with DAN. The HbA1c levels were higher preoperatively in patients with DAN when compared to ND patients and DM patients without DAN. The blood sugar levels were significantly higher in patients with DAN among the three groups which could indicate the association of uncontrolled diabetes with DAN.

According to the study done by Gottschalk A et al. (2014), spinal anesthesia was found to attenuate the hyperglycaemic response in diabetic and ND patients[18] which correlates to the current study.

Amiri F *et al.* (2014) in his study found out that blood glucose level changes caused by surgical stress were not significantly different in the diabetic and ND under spinal anesthesia patients[19] which corresponds to the current study.

Thus, the result of the current study concludes that the blood sugar level showed little change and was more stable during spinal anesthesia perioperatively. The sympathetic blockade produced by spinal anesthesia diminishes the stress response induced physiological changes in various systems like cardiovascular and endocrine systems.[20] Spinal anesthesia causes inhibition of the sympathetic system resulting in a significant decrease in cortisol level, adrenergic system activity and inhibition of renin angiotensin aldosterone system, thereby helping to maintain a stable blood glucose level perioperatively.

The current result is also supported by the study performed by Pflug AE *et a*l. (1981)[21] who demonstrated that surgery induced stress and the resulting hyperglycaemia which was produced by the pain stimulus from the afferent nerves at the tissue injury site, was inhibited by spinal anesthesia; thus, the perioperative and postoperative increase in stress hormones were not observed. Also, in the current study blood sugar level showed similar trends in patients with DAN as in DM patients without DAN signifying no impact of DAN on blood sugar level.

Temperature

According to the current study, the temperature was higher in diabetic patients with autonomic neuropathy initially and had a higher fall in temperature perioperatively. On the other hand, non-diabetic patients and diabetic patients without autonomic neuropathy showed comparable values of fall in temperature perioperatively. The difference in temperature between diabetic patients with autonomic neuropathy and non-diabetic patients was statistically significant ($p \leq 0.05$) for all time intervals (except at T=15 minutes, T=20 minutes, and T=after surgery). This shows that patients with DAN had a low tendency to maintain core body temperature perioperatively.

Kenny G et al. (2016) in his study found that Type 1 and 2 diabetes mellitus are both associated with diminished ability to maintain core body temperature[22] during thermal stress which correlates to the current study.

Kitamura A et al. (2000) in his research found that DAN is associated with a severe perioperative decrease in body temperature[23] which corresponds to the current study.

Therefore, the present study concludes that diabetic patients have a higher resting body temperature and DM patients with DAN are more prone to develop hypothermia perioperatively. The increased resting body temperature might be attributed to the higher body fat mass in diabetic patients in whom a given amount of heat storage per unit mass of body causes a greater increase in core body temperature. Also, obese people have a small body surface area to body mass ratio resulting in ineffective evaporation of sweat.

Previous studies have shown that heat tolerance is impaired in obese patients.[24] Perioperative hypothermia in patients with DAN may be associated with the disability of the body to increase heat production by metabolic factors or decrease blood flow to the skin via vasoconstriction.[22]Autonomic neuropathy may slow down the onset of feedback thermoregulatory constriction of blood vessels and may diminish its effectiveness once activated.[23]

LIMITATIONS

The study has several limitations. Firstly, subjects were not randomized according to the duration of diabetes. HbA1c, an indicator of long-term diabetes control, though measured, was not correlated to the extent of autonomic neuropathy, limiting our understanding of the relationship between diabetes control and autonomic dysfunction. Secondly, we could not measure stress hormone levels (such as cortisol), and we only tracked blood glucose till the procedure was over i.e., immediately after surgery, limiting our understanding of long-term effects and other stress response parameters. The causal relationship between infections and hyperglycemia was not explored as well. The study was also focused on elective surgeries undergoing spinal anesthesia in diabetic and non-diabetic patients, so it may not apply to other patient groups or surgeries. Thirdly, the sample size is relatively small. Also, the study used only one test for autonomic function, which may have underestimated the presence of cardiac autonomic neuropathy. Finally, Other factors that can affect stress response and blood glucose levels, such as intraoperative pain, and effects of various drugs administered intraoperatively were not explored. Surgical stress levels varied among different surgery types, introducing potential variations in blood sugar levels.

CONCLUSION

The present study analyzed various parameters like heart rate, mean blood pressure, blood sugar level and temperature to compare the variation in stress response after neuronal blockade by spinal anesthesia in diabetics versus non-diabetic patients and also to assess the extent of alteration in stress response in patients with DAN under spinal anesthesia.

Amongst the various parameters evaluated, the current study concludes that-

1) Resting heart rate (HR) was significantly increased in patients with DAN. Also, HR showed little variation over time perioperatively in patients with DAN.
2) MBP was increased in DM patients with DAN perioperatively with little change over time.
3) The blood sugar levels remain comparable to the base line perioperatively in all the three groups.
4) The temperature was higher in diabetic patients with autonomic neuropathy initially and had a higher fall in temperature compared to the other groups perioperatively.

Contrarily, the stress response under spinal anesthesia showed no significant change and was comparable in ND patients and DM patients without DAN. The current study provides a better understanding of the correlation between stress response and patients with DAN perioperatively. The study concludes that there is a difference in the parameters of stress response in patients with DAN as compared to DM patients without DAN and ND patients. This difference contributes to a greater risk of morbidity in such patients. To minimize the risk of complications perioperatively and postoperatively, careful monitoring to keep the stress levels under check should be done for patients with DAN.

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