Effect of Lignocaine with and without Adrenaline on Blood Glucose Concentration in Patients Undergoing Extractions

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Abstract

Aims: This study aims to compare the changes in blood glucose concentration following administration of lignocaine with and without adrenaline as local anaesthetic agent for the patients undergoing dental extraction procedure.

Material and methods: This double blind study was carried out in a total of 175 individuals. These individuals were divided into two groups as experimental group consisting 150 healthy individuals and undergoing multiple extractions and control group consisting of 25 individuals who didn't need any dental extractions. Blood glucose concentrations were measured pre-operatively immediately, 10min, 20min and 30 min after the injection of the lignocaine once with and another time without adrenaline in two separate appointment with minimum of 7 days interval.

Results: In patients who received plain lignocaine without adrenaline there was a decrease in the blood glucose concentration except for mild hyperglycaemia immediately after administration of plain lignocaine. Whereas in patients who received lignocaine with adrenaline there was increase in blood glucose concentration at all times.

Conclusion: We conclude that adrenaline containing clinical doses of lignocaine exerts systemic metabolic response in normal healthy patients and increase the blood glucose concentration as outlined in this study.However we are unable to comment regarding the decrease in blood glucose concentration following administration of lignocaine without adrenaline.

Clinical significance: Since the increase in blood glucose concentration according to our study is quite significant, lignocaine with adrenaline need to be used very cautiously in non- insulin dependent diabetic patients.

Key words- lignocaine, adrenaline, blood glucose concentration, systemic effects.

Introduction

Dentistry has always been associated from times immemorial, with pain. The dental surgeon has to resort, frequently, to inject local anaesthetics to control intra-operative pain. An oral surgeon has to, by and large, use local anesthetics for most minor surgical procedures.

In our country, lignocaine hydrochloride is the most widely used and easily available local anaesthetic agent. Adrenaline is frequently combined with lignocaine to enhance the duration of anaesthesia, decrease toxicity, to achieve vasoconstriction and to provide a bloodless field.

Since lignocaine with or without adrenaline is one of the most commonly used local anaesthetic in our country, we decided to undertake a study to observe its effects on blood glucose concentration in healthy patients undergoing extractions.

There is considerable information available in literature concerning the haemodynamic effects of vasoconstrictors in dental local anaesthetic solutions[1], in both healthy and medically compromised individuals. There is however little data on systemic metabolic effects attributable to the injection of local dental anaesthetics.

It has been generally accepted that low concentration of adrenaline in anaesthetic solution does not produce any systemic effects. However, though the volumes injected are small, the oral area is highly vascular resulting in haemodynamic and metabolic changes.

This study is the evaluation of effects of lignocaine with or without adrenaline on blood glucose concentration in patients who underwent dental extractions in our institute.

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Materials and Methods

The study comprised of study group and control group, the study group included 150 healthy medically uncompromised patients who were in need of multiple dental extractions, were not under any medications, had no history of any systemic disorders and were in the age group of 14- 40 years.

25 healthy volunteers of age group 14-40 years who did not need dental extraction were included in the study as control group.

Selection criteria for study group

1. Patients who were healthy and did not have any systemic disorders and willing to participate in the study.
2. Patients needing multiple extractions.
3. Patients who were not on any other medications.
4. Patients in age group of 14-40 years.

Selection criteria for control group:

1. Patients who were healthy and did not have any systemic disorders and were willing to participate in the study.
2. Patients not needing any extractions.
3. Patients who were not on any other medications.
4. Patients in the age group of 14-40 years.

In the selection of both study and control group the above protocols were
followed. After selection of the patients consent was obtained from these patients.

Method of blood glucose estimation- (Figures 1-6)

The patient was seated comfortably and subjected to thorough anamnesis. The first reading of the blood glucose concentration was taken before administration of local anaesthesia by pricking the tip of the finger with sterile lancet. Peripheral blood glucose was estimated by using a glucometer. 4.4 ml of local anaesthetic agent (once plain lignocaine and second time lignocaine with adrenaline with week's interval in between) was administered[2] in the form of nerve block.

Immediately after administration of local anaesthesia, peripheral blood glucose estimation using glucometer was done. Next readings were obtained after 10 min, 20 min and 30 min post injection. Readings were noted in mg/dl and compared with the readings taken before giving L.A and analyzed. In both the groups series of peripheral blood glucose concentration were estimated using glucometer. But the only difference was that in study group the patients were exposed to surgery giving the block of 4.4 ml of L.A with and without adrenaline at two different appointments as explained above and the series of peripheral Blood glucose concentration were estimated and compared with the sample of peripheral blood glucose concentration taken before giving L.A. Where as in control group the same procedures were carried out but patients were not exposed to any type of surgery.

Principles of blood glucose estimation using glucometer-

The device used for blood glucose concentration were Gluco accutrend meter, Gluco accutred test strips, Soft clix II finger pricking device manufactured by Borhringer Mannheim, a german based company. It is the result of extensive research among patients in U.K. it is been designed to make testing virtually painfree. It is simple and accurate, making the necessity of monitoring as little a burden on day-to-day life as possible. Unlike many meters the gluco accutrend meter is able to read a minimal sample (just 3 microliter).

Test principle-

Glucose oxidase/ mediatory reaction accutrend glucose test strips react specifically to glucose. It works on the glucose oxidase and peroxidase method of glucose estimation. Glucose oxidase in the reagent acts with glucose in blood serum in the presence of oxygen to give gluconic acid and hydrogen peroxide. Peroxidase breaks hydrogen peroxide to water and oxygen. Oxygen that is liberated is accepted by the chromogen system to give guinoneimina (a red color compound). The red color so developed is proportional to the blood glucose concentration and is measured photo-metrically at 5.05 nm WL (500-540 nm WL) or with green filter.

Reactions occurs as follows

Glucose + oxygen +H2O+ glucose oxidase ---- gluconate +H2O2

H2O2 +phenol+ 4amino antipyrlene peroxidase chrome + H2O complex

Blood glucose estimation were done at pre-injection, post- injection and at intervals of 10 min, 20 min, 30 min postoperatively with adrenaline and without adrenaline , and changes in the level of glucose concentration were compared by analysis of paired 't' test and Wilcoxon's signed rank test.

Results

This study aimed to compare the blood glucose concentration in patients who were administered lignocaine with and without adrenaline in two categories of groups. Study group: consisting of 150 healthy subjects undergoing dental extractions of which 87 were males and 63 were females within the age group 14-40 years with average age being 28 years. Control group: consisting of 25 healthy subjects (not undergoing any dental extractions) of which 20 were males and 5 were females within the age group 14-40 years with average being 22 years.

The blood glucose concentration irrespective of stress rose during the dental extraction procedures when lignocaine with adrenaline was administered (graph 1 and 2).

Table 1: shows the results of blood glucose concentrations of the patients which were administered plain lignocaine in the study group and control group recorded at 5 intervals. In study group mean blood sugar was 84.47±16.56 rose to 84.68±16.47, a difference of 0.21mg/dl from base line which was not significant, similar to the sample take at 10th and 20th minute. Whereas sample taken at 30th minute was significant with difference of -1.38 mg /dl from base line (P<0.05)

Table 2: shows the blood glucose concentrations in the patients which were administered lignocaine with adrenaline in the study and control group at 5 intervals. In the study group blood glucose concentration was maximum after 30 minutes after local anaesthesia i.e. 106.16 followed by 20 and 10 minutes and immediately after local anaesthesia in decreasing order. All these values were highly significant when compared to baseline values (P< 0.001).

In the control group blood glucose concentration was also maximum after 30 minutes 101.84 ± 22.96 followed by the readings at 20 minutes, 10 minute immediately and before L.A in decreasing order. These values were highly significant when compared with base line values (P< 0.001).

Table 3: shows comparison between lignocaine and lignocaine with adrenaline (study group) difference in the blood glucose concentration when compared with and without adrenaline among study group was statistically significant at the 10 minute reading difference in the means was 5.03 (P< 0.005).

Highly significant difference in values was found at 20 and 30 minutes intervals difference in the means was 19.22 and 23.07 respectively (P <0.001)

Table 4: shows comparison of blood glucose concentration between plain lignocaine and lignocaine with adrenaline in control group.

Blood glucose concentration was more in lignocaine with adrenaline group when compared to plain lignocaine with a difference in the means of 13.8 at 10 minutes reading. This was statistically significant (P<0.05).

Difference in the blood glucose concentration was highly significant at 20 minutes and 30 minutes reading (18.6 and 25.8 respectively) (P<0.001).

Table 5: shows comparison of mean changes in blood glucose concentrations between plain lignocaine and lignocaine with adrenaline in study group. Difference in the mean changes between lignocaine with adrenaline and plain lignocaine was maximum from base line to 30 minutes reading i.e. 21.08 which was statistically significant (P<0.001) followed by baseline to 20 minutes and baseline to 10 minutes (17.3 and 10.3 respectively). These values were also statistically significant (P<0.001).

Difference in the mean changes was also statistically significant from baseline to immediately taken reading (P<0.05).

Table 6: shows comparison of mean changes in blood glucose concentrations between plain lignocaine and lignocaine with adrenaline in control group. The compared values were highly significant at 30, 20 and 10 minutes (21.6, 14.2, 8.9) (P<0.001).

But the difference mean change was not significant when compared to the immediately taken sample.

Table -1 (Plain lignocaine)

Time	Study group				Control group			
	Mean blood sugar	Diff From BL	% change	Sig*	Mean blood sugar	Diff From BL	% change	Sig*
Before LA	84.47 ± 16.56	-	-	-	76.40 ± 8.24	-	-	-
After LA	84.68 ± 16.47	0.21	0.3	NS	76.80 ± 8.71	0.40	0.5	NS
10 min	84.64 ± 16.58	0.17	0.2	NS	76.68 ±9.73	0.28	0.4	NS
20 min	84.17 ±16.64	-0.30	0.4	NS	76.88 ±9.40	0.48	0.6	NS
30 min	83.09 ± 16.17	-1.38	-1.6	P<0.05	76.00 ± 8.46	-0.40	-0.5	NS

Table 2. (Lignocaine with adrenaline)

Time	Study group				Control group			
	Mean blood sugar	Diff From BL	% change	Sig*	Mean blood sugar	Diff From BL	% change	Sig*
Before LA	86.46 ± 19.83	-	-	-	80.60 ± 21.95	-	-	-
After LA	87.96 ± 18.74	1.50	1.7	HS	81.92 ±20.28	1.32	1.6	Sig
10 min	96.93 ± 21.61	10.47	12.1	HS	89.76 ± 21.72	9.16	11.4	HS
20 min	103.46 ± 24.39	17.00	19.7	HS	95.28 ± 20.72	14.68	18.2	HS
30 min	106.16 ± 25.76	19.70	22.8	HS	101.84 ± 22.96	21.24	26.4	HS

Negative sign indicates reduction in blood glucose concentration
***Paired 't' test LA- Local anaesthesia BL -Base Line P<0.05 significant, P<0.001 Highly significant**

Table 3.(Comparison of blood glucose concentration between plain lignocaine and lignocaine with adrenaline in study group)

Time	Plain lignocaine		Lignocaine with adrenaline		Difference	Significance
	Range	Mean: t SD	Range	Mean t SD		
Before LA	50- 134	84.47 ± 16.56	50-157	86.46 ± 19.83	1.99	NS
After LA	50- 135	84.68 ± 16.47	56-149	87.96 ± 18.74	3.28	NS
10 min	55- 137	84.64 ± 16.58	61-158	96.63 ±21.61	5.03	Sig (P<0.05)
20 min	50- 129	84.17 ±16.64	50-164	103.46 ± 24.39	19.22	HS (P< 0.001)
30 min	50- 128	83.09 ± 16.17	58-162	106.16 ± 125.79	23.07	HS(P<0.001)

Table 4. (Comparison of blood glucose concentration between plain lignocaine and lignocaine with adrenaline in control group)

Time	Plain lignocaine		Lignocaine with adrenaline		Difference	Significance
	Range	Mean: t SD	Range	Mean t SD		
Before LA	61- 90	76.40 ±8.24	53-147	80.60 ± 21.95	4.20	NS
After LA	63- 94	76.80 ±8.71	58-145	81.92 ±20.28	5.12	NS
10 min	64- 92	76.68 ±9.73	50-151	89.76 ±21.72	13.08	Sig (P<0.05)
20 min	62- 96	76.68 ±9.40	58-161	95.28 ±20.72	18.60	HS (P< 0.001)
30 min	61- 101	76.00 ± 8.46	76-169	101.84 ± 22.96	25.84	HS(P<0.001)

(Z – Test) (Unpaired t – Test) P< 0.05 significant P<0.001highly significant

Table 5. (Comparison of mean changes in blood glucose concentration between two groups in study group)

Time Interval	Mean difference from baseline		Difference in mean changes	Significance*
	Plain lignocaine(A)	Adrenaline (B)		
Baseline t I ALA	+ $0.21_{\pm 3.38}$	+ $1.50_{\pm 4.81}$	1.29	P<0.05
baseline t 10 mm	+ $0.17_{\pm 6.63}$	+ $10.47_{\pm 11.79}$	10.3	P<0.001
baseline t 20 mm	-$0.30_{\pm 7.92}$	+ $17.00_{\pm 16.08}$	17.3	P<0.001
baseline to 30 min	-$1.38_{\pm 7.61}$	+ $19.70_{\pm 16.55}$	21.08	P<0.001

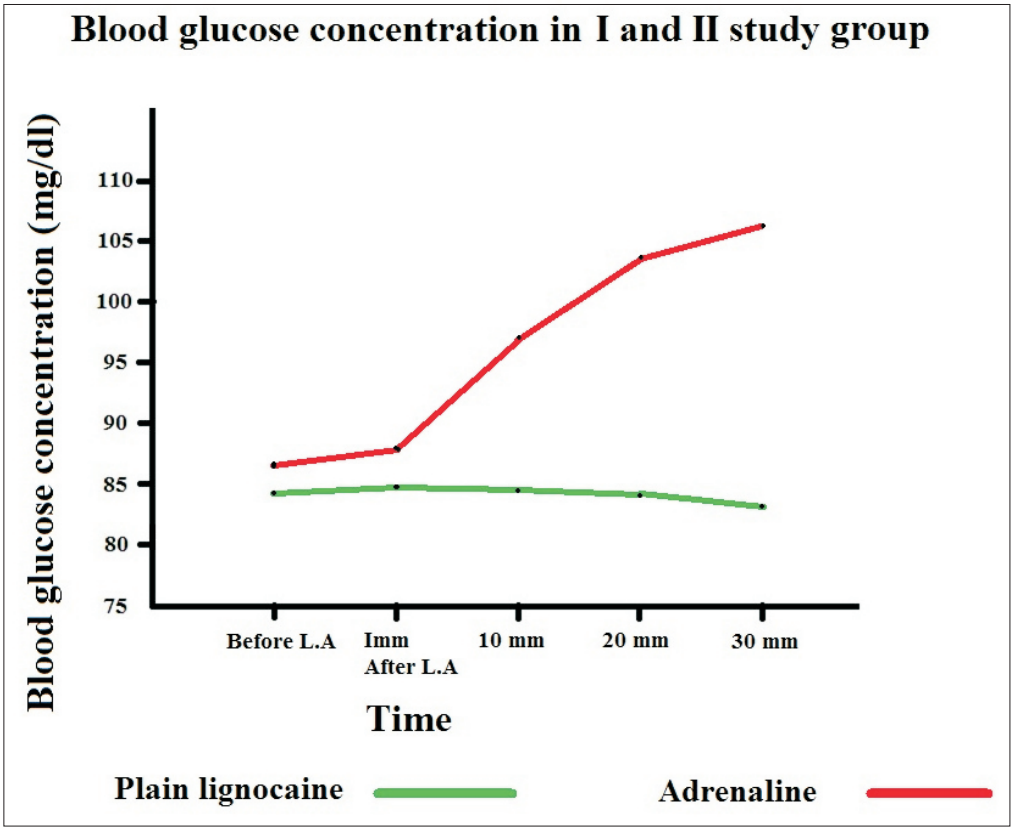
Z – test P<0.05 – significant P<0.001 – highly significant

Table 6. (Comparison of mean changes in blood glucose concentration between two groups in control group)

Time interval	Mean difference from baseline		Difference in mean changes	Significance*
	Plain lignocaine(A)	Adrenaline (B)		
Baseline t I ALA	+ $0.40_{\pm 2.33}$	+ $1.32_{\pm 3.06}$	0.92	NS
baseline t 10 mm	+ $0.28_{\pm 3.51}$	+ $9.16_{\pm 10.91}$	8.98	HS
baseline t 20 mm	+$0.48_{\pm 2.51}$	+ $14.68_{\pm 7.57}$	14.20	HS
baseline to 30 min	-$0.40_{\pm 2.70}$	+ $21.24_{\pm 11.36}$	21.64	HS

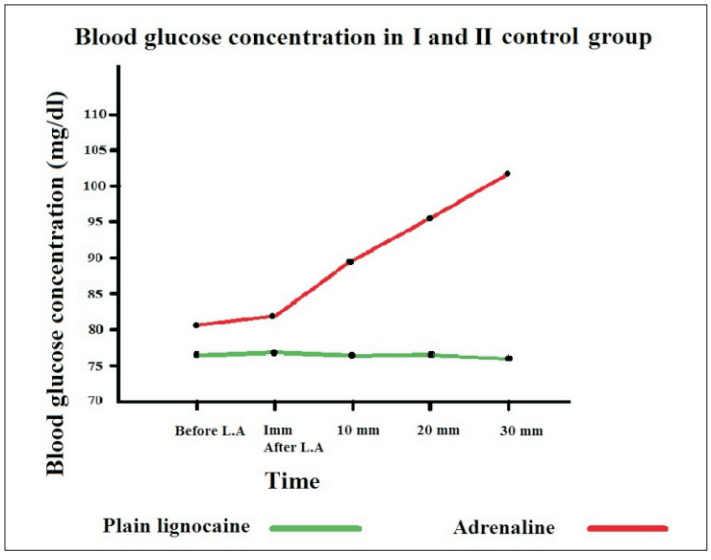
***unpaired t test HS – highly significant (P<0.001) NS – not significant**

Graph 1



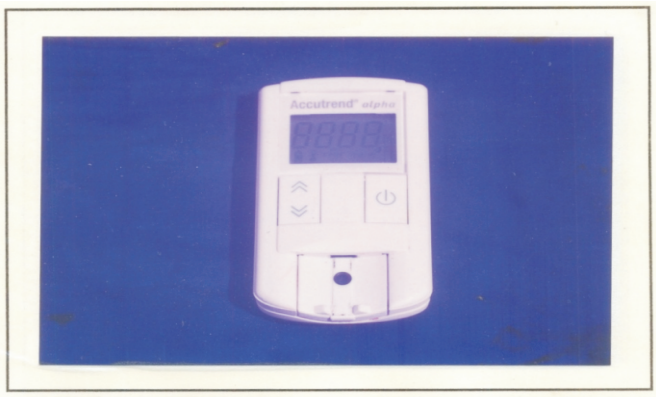
I group – plain L.A II group – L.A with adrenaline

Graph 2

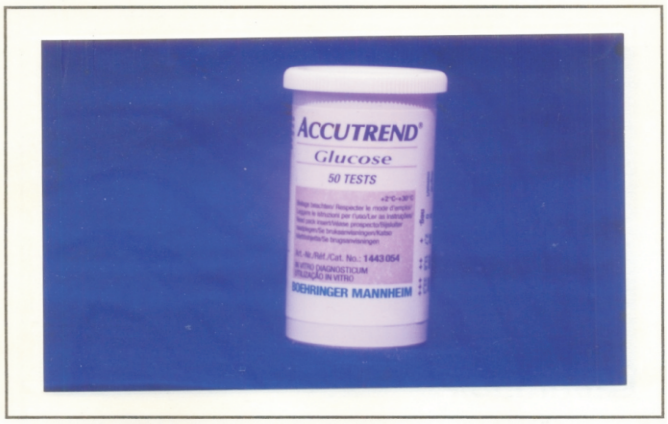


I group – plain L.A II group – L.A with adrenaline

Graph 1 and 2. Blood glucose concentration in I and II study group

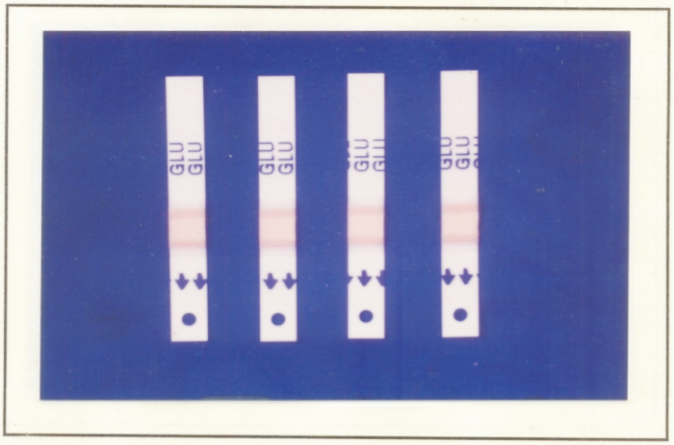


DIGITAL GLUCOMETER

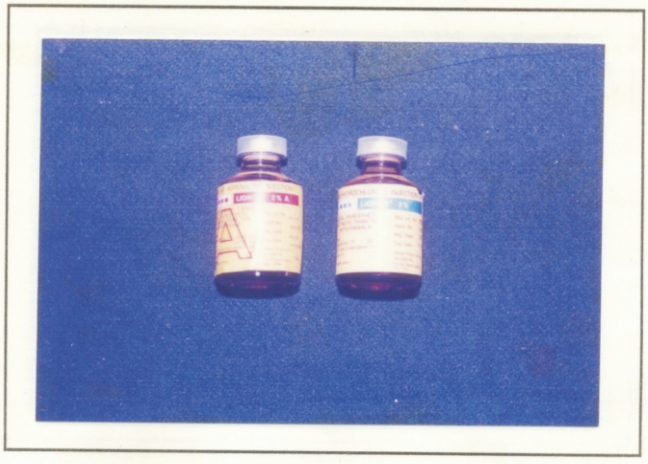


TEST STRIP BOX

Figure 1 and 2

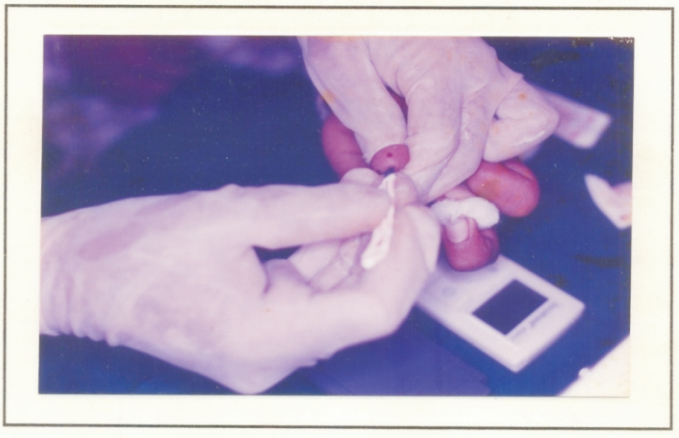


TEST STRIPS

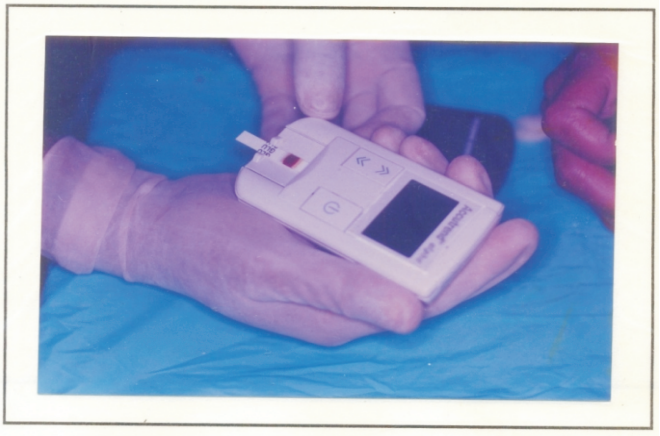


LIGNOCAINE WITH & WITHOUT ADRENALINE

Figure 3 and 4



PRICK BEFORE RECORDING GLUCOSE LEVELS



STRIP IN GLUCOMETER AFTER LOADING BLOOD

Figure 5 and 6

Discussion

Various studies have been done on the effect of plain lignocaine and lignocaine with adrenaline on systemic functions and metabolic implications. These studies provided the information regarding hemodynamic changes following administration of local anaesthetic agents.

In 1988 a double blind study was carried out to evaluate the hemodyanamic effects and plasma catecholamine concentration after administration of local anaesthesia with adrenaline and concluded that plasma catecholamines increased 10 fold from 0.02(+/-0.02) to 1.02 (+/-0.3) nmol/litre,following administration of lignocaine with adrenaline.[3]

In 1982 goldstein et al reported the hyperglycemic effects of adrenaline containing local anesthetics occur at plasma adrenaline concentration 4-5 times the basal levels after 5 minutes post injection.[4] such an observation was also reported shortly after injection of adrenaline containing local anesthesia administered in clinical dose [1].

In the present study an effort was made to evaluate the blood glucose levels in patients undergoing extractions in the age group 14-40 years (study group- 150 patients and control group- 25 healthy volunteers) injected with local anaesthesia with and without adrenaline. A standard protocol was followed and dental extractions were done. The procedures were completed within 30 minutes. Each patient was subjected to a similar procedure under local anaesthesia containing 1:80,000 adrenaline and found that 150 patients, 25 healthy volunteers had a period of transient hyperglycaemia following injection, where as when 2% lignocaine without adrenaline was used during surgery though there was hyperglycaemia immediately after injection, it was clinically insignificant. The blood glucose increased from mean baseline values of 84.47 +/- 16.36 to 84.68 +/- 16.4 (sample taken immediately after plain local anaesthesia administration). (refer table no.1) and may be attributed to the stress related endogenous catecholamine release, whereas the values observed 30 minutes after administration of plain lignocaine in study group was significantly less than baseline values.The difference between the mean blood glucose level and the blood glucose levels recorded after 30 minutes had a difference of -1.38 ($P < 0.05$), though clinically significant the difference was negligible. In control group the difference from the baseline value was -0.40 which was not significant.

Whereas in cases of lignocaine with adrenaline there was a highly significant increase in the blood glucose concentration when recorded immediately after injection, followed by similar significant rise in the glucose concentration at intervals of 10^{th}, 20^{th} and 30^{th} minute post injection of local anesthetic with adrenaline. This feature of significant elevation in blood glucose concentration immediately after administration of LA was seen in both the groups of patients (study group and control group).

In cases of study group the blood glucose concentration increased from 84.46 mg/dl (+/- 19.83 base line value) to 106.16 mg/dl (+/- 25.79 mean value) for the sample taken after 30 minutes. Similar elevation in blood glucose concentration was observed in control group which increased from 80.60 mg/dl (+/- 21. 95 baseline value)to 101.84 mg/dl (± 22.96 mean value) taken after 30 minutes.

In short in both the groups where lignocaine with adrenaline was used there was a transient and significant increase in blood glucose concentration [1].

When the same was done with plain lignocaine, without adrenaline, in both the groups the blood glucose levels decreased and went below the base line values except when taken immediately after injection of local anaesthesia where as blood glucose levels increased in cases of local anaesthesia with adrenaline. Such increase in the blood glucose level in the patients receiving local anaesthesia with adrenaline can be solely contributed to the adrenaline in local anaesthesia, which was observed by Meechan J.G 1991 [2].

This increase in blood glucose concentration is due to adrenergic stimulation of adrenaline in local anaesthetic solution. Sympathomimetic amines such as epinephrine exerts their effects by interacting functionally with several different adrenergic receptors [2]. These include $\alpha 1$, $\beta 1$, $\beta 2$ receptors which are found throughout the body. Epinephrine is a potent stimulator of both α and β activity.

Stress is also known to increase blood glucose levels. Stress caused by needle puncture and injection

may have contributed. Since we have taken a control group (not undergoing extraction) and taken care to take blood glucose levels of patients in study group (needing extraction) prior to extraction, the effects of the stress has more or less evened out. The role of stress was evaluated more efficiently in 1984 in the study which evaluated circulating adrenaline levels in sedated and non- sedated patients having third molar surgery under local anaesthesia with and without adrenaline [5,6].

Rizza et al concludes that epinephrine increases glucose production and plasma glucagon transiently but suppressed glucose clearance [7].

Peter C. Butler et al states that catecholamines increase glucose production by stimulating glycogenolysis and gluconeogenesis. In contrast to glucagon, catecholamines cause a more sustained increase in blood glucose concentrations by decreasing glucose utilization, both directly by affecting peripheral tissue glucose uptake and indirectly by decreasing insulin release [8].

In a nutshell adrenaline increases blood glucose concentration probably due to the following reasons-

1. Reduction in insulin secretion by the action of α2 adreno-receptors causing inhibition of β cells of islets of langerhans in pancreas [8,9].
2. Action of α 1a and α 2b in the liver stimulating gluconeogenesis [10] by increasing substrate concentration as well as by increasing glucagons and decreasing insulin secretion [8,11].
3. Stimulation of glycogenolysis via adrenergic stimulation of β receptors resulting in a cyclic AMP dependent activation of phosphorylation [8].
4. Decrease in glucose utilization both directly by effecting peripheral tissue glucose uptake and indirectly by decreasing insulin release [8,9].
5. Beta adrenergic mediated increase in glucagons concentration. Glucagon increases the glucose production by stimulating glycogenolysis, gluconeogenesis [10] and inhibiting hepatic glycolysis. Glucagons stimulate glycogenolysis through a cyclic AMP dependent mechanism that results in a reciprocal increase in phosphorylase and a decrease in glycogen synthetase activity. As insulin has the opposite effect on the activity of these enzymes through a cyclic AMP independent mechanism, the prevailing ratio of glucagons and insulin concentration of the blood in the portal vein is presumably important in determining hepatic glucose balance [8,10].
6. Other beta-adrenergic effects causing stimulation of lypolysis and ketogenesis, which may indirectly serve to decrease glucose uptake [8].
7. Increase in lactate concentration due to beta adrenergic stimulation of skeletal muscles glycogenolysis, which thus becomes available for hepatic gluconeogenesis [10].

Since we have subjected the same patients under the same set of circumstances, time, nutrition and environment to injections of plain lignocaine and lignocaine with adrenaline, the settings can be considered to be standardized. The hyperglycaemic responses to lignocaine with adrenaline can therefore be safely attributed to the action of adrenaline alone, probably due to the actions outlined above. Therefore it can be accepted that adrenaline in lignocaine thus causes an increase in blood glucose concentration [1].

Conclusion

In this study adrenaline present in local anesthesia is a main source of adrenergic stimulation. Increase in blood glucose concentration in immediately taken sample when injected with plain lignocaine can be attributed as stress related hormonal response and endogenous catecholamine release which invariably results in hyperglycaemic episode. However we were unable to come to a conclusion regarding the decrease in blood glucose concentration following injection in the sample taken at 30th min i.e - 1.38 mg/dl difference with baseline value would be very negligible.

The sustained elevations in blood glucose concentrations observed in the present study is attributed to injections of adrenaline containing local anesthetics, that is exogenous adrenaline as well as stress related catecholamine release probably a combination of both following adrenaline containing

L.A injections. It is our conclusion that an adrenaline containing lignocaine solution injected in clinical doses exerts systemic metabolic responses in normal patients namely increases in blood glucose concentration as out lined in the study. The effect of blood glucose elevations in this study is unlikely to be hazardous per se but it may be considered as a marker of systemic metabolic effects of exogenous adrenaline.

Clinical significance

This hyperglycemic effect of adrenaline may not pose any danger to normal patients but would definitely be a cause of concern to patients with non-insulin dependent diabetes.

Therefore plain lignocaine may be used without any fear of increase in blood glucose level in healthy patients, whereas lignocaine with adrenaline will definitely cause an increase in blood glucose level. So as the increase in blood glucose concentration according to our study is quite significant, lignocaine with adrenaline need to be used very cautiously in diabetic patients.

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