

THE EFFECTS OF TWO DIFFERING TECHNIQUES ON THE ACCURACY OF REAGENT STRIP BLOOD GLUCOSE TESTING

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Keywords: reagent strips; blood glucose; hypoglycaemia; alcohols; reflectance photometer

ABSTRACT

The use of 70% isopropyl alcohol to prepare the site of skin puncture for reagent strip blood glucose testing has been reported to produce falsely elevated blood glucose levels. The objective of this study was to identify if any significant difference existed between the capillary blood glucose levels of healthy volunteers tested using a capillary blood glucose reagent test strip and reflectance photometer, comparing results obtained (i) with and without the use of 70% isopropyl alcohol to prepare the site of skin puncture and results obtained (ii) with and without 70% isopropyl alcohol using the first and second drops of blood. Data analysis revealed a significant interaction between the two factors specified above. If 70% isopropyl alcohol is used to prepare the skin there is a significant elevation of 0.39 mmol/l in mean blood glucose concentration between results obtained using the first and second drops of blood while if the first drop of blood is used there is a significant elevation in mean blood glucose concentration of 0.49 mmol/l between results obtained using and not using 70% isopropyl alcohol to prepare the skin.

OPSOMMING

Volgens 'n verslag het die gebruik van 70% isopropyl alkohol om die plek van velpunktuur vir reagensstrook bloedglukosetoetsing voor te berei valslikverhoogde bloedglukosevlakke geproduseer. Die doel van hierdie studie was om vas te stel of daar enige beduidende verskille bestaan tussen die kapillêre bloedglukosevlakke van gesonde vrywilligers wat getoets is deur van 'n kapillêre bloedglukose-reagenstoetsstrook en weerkaatsingsfotometer gebruik te maak, en die resultate wat verkry is te vergelyk (i) met en sonder die 70% isopropyl alkohol om die plek van velpunktuur voor te berei en resultate wat verkry is (ii) met en sonder 70% isopropyl alkohol deur die eerste en tweede druppels bloed te gebruik. Data-analise het 'n betekenisvolle interaksie aangedui tussen die twee faktore hierbo gespesifiseer. Indien 70% isopropyl alkohol gebruik word om die vel voor te berei is daar 'n betekenisvolle verhoging van 0.39 mmol/l in die gemiddelde bloedglukosekonsentrasie tussen resultate wat gebruik is deur die eerste en tweede druppels bloed te gebruik terwyl indien die eerste druppel bloed gebruik is daar 'n betekenisvolle verhoging is in die gemiddelde bloedkonsentrasie van 0.49 mmol/l tussen die resultate wat verkry is deur 70% isopropyl alkohol te gebruik en nie te gebruik nie om die vel voor te berei.

INTRODUCTION

Capillary blood glucose reagent test strip analysis is widely used to determine capillary blood glucose concentrations and guide the treatment of patients suspected of being hypoglycaemic. These simple tests are invaluable in rapidly providing a level of accuracy in the testing of blood glucose concentration that is regarded as sensitive enough for clinical decision-making (Lavery, Allegra, Cody, Zacharias & Schreck, 1991:305-306; Kumar, Sng & Kumar, 2003:379). Within this context, hypoglycaemia has been variably defined using different lower limits of serum and capillary blood glucose concentrations, ranging from 2.7 mmol/l (Fischer, Lees & Newman, 1986:1245) to 3.5 mmol/l in adults (Professional Board for Emergency Care Practitioners, 2006:48) and a lower limit in neonates of 1.7 mmol/l (Sieber & Traytsman, 1991:104).

Hypoglycaemia is a common emergency in both the hospital (Fischer, Lees & Newman, 1986:1246; Feher, Grout, Kennedy, Elkeles & Tourquet, 1989:184; Mendoza, Kim & Chernoff, 2005:93-94) and pre-hospital environments (Holstein, Plaschke, Vogel & Egberts, 2003:612-614). Several observational studies have shown that prolonged hypoglycaemia and neuroglycopenia may result in permanent neurological sequelae and, infrequently, death (Fischer *et al.* 1986:1246; Feher *et al.* 1989:184; Young, 1998:333-334; Holstein *et al.* 2003:612-614; Mendoza *et al.* 2005:93-94). Although randomised, large scale and well-controlled studies of the effects of hypoglycaemia on mortality and morbidity are lacking, the damaging effect of hypoglycaemia on neurons in the laboratory setting has been established (Auer, 1986:703; Sieber & Traytsman, 1991:104-107; Young, 1998:334-335).

Not all patients presenting with a serum or capillary blood glucose concentration below a given threshold will require supplemental glucose (Fischer *et al.* 1986:1246). As a result, the term "symptomatic hypoglycaemia" has been used to describe a capillary or serum glucose concentration below a specified limit together with clinical features attributable to this glucose deficient state, indicating the need for supplemental glucose administration. Such clinical features reflect the manifestations of neuroglycopenia and hyperepinephrinaemia (Malouf & Brust, 1985:423; Sieber & Traytsman, 1991:104-107). Unfortunately,

placing sole emphasis on symptomatic manifestations of hypoglycaemia without measurement of serum glucose concentration is neither sufficiently sensitive nor specific in the identification of hypoglycaemic patients who may be at risk for developing neurological damage (Hoffman, Schringer, Votey & Luo, 1992:21-22; Hansen & Simpkins, 1980:681-682).

Considering the potentially damaging neurological effects of neuroglycopenia, it may be argued that the mere suspicion of hypoglycaemia, whether through symptoms or patient history, should validate the administration of supplemental glucose in the absence of quantitative measures of serum or capillary blood glucose concentration. However, the possible dangers of such "blind" supplemental glucose administration and risk of resultant hyperglycaemia, particularly in the setting of cerebral ischaemia, have been suggested by several experimental animal and observational human studies (Pulsinelli, Waldman, Rawlinson & Plum, 1982:1241-1243; Nakakimura, Fleischer, Drummond, Scheller, Zornow, Grafe & Shapiro, 1990:1007-1008; Michaud, Rivara, Longstreth & Grady, 1991:1357; Sieber & Traytsman, 1991:104-107; Rovlias & Kotsou, 2000:338-340). Thus, rapid supplemental glucose administration in hypoglycaemia is essential in preventing permanent neurological damage, but only after positive identification of a low serum or capillary blood glucose concentration. For this reason, testing of capillary blood glucose concentration using reagent strips in cases of suspected hypoglycaemia is currently recommended in the pre-hospital setting (Professional Board for Emergency Care Practitioners, 2006:48) and is also widely used for bedside blood glucose monitoring in hospitals and for self-testing of blood glucose concentration by diabetic patients.

Although commercially available reagent test strips used for blood glucose analysis have generally been found to be accurate in detecting clinically significant degrees of hypoglycaemia (Pepe, Ginger & Ritter, 1990:313; Jones, Ray, Gough, Garrison & Whitley, 1992:680-681; Scott, Wolf & Spadafora, 1998:306; Holstein *et al.* 2003:612-614) a number of variables have been suggested to affect the accuracy of the test strip results. These variables include serum ascorbic acid concentration (Sylvester, Price & Burrin, 1994:95), haematocrit (Dacombe, Dalton, Goldie & Osborne, 1981:782-784), serum bilirubin concentration (Sylvain & Pokorny,

1995:46), paracetamol levels (Sylvester, Price & Burrin, 1994:95), states of low peripheral perfusion such as shock (Atkin, Dasmahapatara, Jaker, Chorost & Reddy, 1991:1022; Sylvain & Pokorny, 1995:46), resuscitation from cardiac arrest (Thomas, Gough, Benson, Austin & Stone, 1994:1073-1074), and isopropyl alcohol used for cleansing of the blood sampling site (Phillips, Pain, To & Ormsby, 1977:790-791; Grazaitis & Sexson, 1980:221-223).

The relevance of the effects of ascorbic acid, bilirubin concentration, paracetamol levels and low peripheral perfusion on test strip accuracy is, to a great extent, academic because the presence of these factors is impossible to predict or avoid in an emergency situation and, once in existence, generally cannot be rapidly removed. Of more practical importance on the other hand, is the effect that skin preparation with isopropyl alcohol has on test strip accuracy. Manufacturers of a widely used capillary blood glucose reagent test strip (Haemo-glukotest 20-800R®) recommend that, whether or not a disinfectant is used to prepare the blood sampling site, the skin be allowed to dry before obtaining the blood sample otherwise "erroneous results" may be obtained. In addition, it is recommended that the first drop of blood obtained after skin puncture be wiped away, and the second drop of blood be placed on the reagent test strip (Boehringer Mannheim, 1992). Unfortunately, no references are provided in the product information leaflet to support these recommendations nor to give an indication of the magnitude or clinical significance of the purported error.

There exists no universal, interdisciplinary standard for the teaching and practice of capillary blood glucose reagent strip testing, specifically with reference to the two aspects of the technique specified above. It can therefore be expected that a degree of variance will exist in the way this testing is performed by medically trained personnel and by patients themselves and that this will be determined by local practice. There is also a lack of scientific data evaluating the clinical significance of any effect on accuracy of the test strip result should practitioners or patients use differing techniques for blood sample collection. Extensive searches of both the US National Library of Medicine's Medline database and the Cumulative Index to Nursing and Allied Health Literature identified only four dated articles suggesting that contamination of a capillary blood sample with iso-

propyl alcohol may produce erroneously elevated results (Ball & Hughes, 1976:1279; Phillips, Pain & Ormsby, 1977:790-791; Grazaitis & Sexson, 1980:221-223; Togari, Oda & Wada, 1987:408-409).

In a letter to the editor of the *British Medical Journal*, Ball and Hughes (1976:1279) report a case where the use of 70% isopropyl alcohol prior to capillary blood sample testing with a reagent strip resulted in an over-estimation of a hypoglycaemic patient's blood glucose concentration, the true value of which was detected with a subsequent laboratory serum glucose assay. Although this is a single case and no other data are presented, the authors contend that the use of alcohol in this way should be avoided in order to prevent the "potential misdiagnosing of hypoglycaemia".

Phillips *et al.* (1977:790-791) evaluated paired capillary blood samples obtained with "wet" and "dry" 70% isopropyl alcohol on the skin surface. No significant difference in blood glucose concentration between the "wet" and "dry" groups was found, but the small sample used ($n = 12$) increases the risk of a Type II error and the results should thus be evaluated with caution. These authors conducted a second set of tests in the same study with blood sampled from one subject. This blood was exposed to 70% isopropyl alcohol on a glass slide and a glass slide without alcohol in thirteen repetitions. Inexplicably, the authors did not perform any kind of statistical analysis on data from this second set of tests, only pointing out that the blood samples exposed to alcohol gave mean glucose measurements 0.1 mmol/l higher than those that were not exposed.

Grazaitis and Sexson (1980:221-223) report a case involving a neonate in whom a heel stick capillary blood glucose concentration measured with a reagent strip and reflectance photometer was 1.5 mmol/l higher than that obtained from central venous blood tested in a laboratory. They point out that the heel stick sample was contaminated with 70% isopropyl alcohol and that this accounted for the higher measured glucose concentration. Following the case report, in the same publication, these authors report on tests conducted by them on reagent test strips by exposing them to pure 70% isopropyl alcohol, venous blood samples and a mixture of venous blood and 70% isopropyl alcohol in a three-to-one ratio. Again, no formal statistical analysis was performed and no reference or explanation is given

for the choice of blood-to-alcohol ratio in the mixture used for testing. The authors only report the mean blood glucose concentration from 20 measurements with a reflectance photometer in each group, noting that the mean blood glucose concentration was 10.6 mmol/l higher in the group of samples where venous blood and isopropyl alcohol were mixed, compared to venous blood not mixed with isopropyl alcohol.

Togari *et al.* (1987:408-409) attempted to isolate the exact biochemical mechanism of the previously reported erroneous effect of isopropyl alcohol on reagent test strips used for capillary blood glucose analysis. As was the case with the study by Grazaitis and Sexson (1980:221-223), isopropyl alcohol, this time in a 45% solution, was deliberately mixed with samples of capillary blood. No statistical analysis was performed to establish significant differences; the authors once again simply referring to the mean differences between blood samples with and without alcohol admixture in support of the assertion that the addition of 45% isopropyl alcohol to capillary blood samples does cause a false elevation in mean blood glucose concentration. No mention is made of the ratio of alcohol to blood mixture in this experiment.

The studies summarised above are flawed and cannot precisely determine the clinical effect of 70% isopropyl alcohol usage on the accuracy of reagent tests strip results. Clearly, the presentation of a case report, although interesting, can never constitute satisfactory evidence for this effect. The large elevation in blood glucose concentration attributed to the effects of isopropyl alcohol in the study by Grazaitis and Sexson (1980) could very well have been caused by the relatively high concentration of alcohol deliberately mixed with the blood samples before testing, something the authors elected to do but did not explain or validate. Furthermore, in this study and in the studies by Phillips *et al.* (1977:790-791) and Togari *et al.* (1987:408-409), data that supposedly established the erroneous effect of isopropyl alcohol on blood glucose test results were not subjected to statistical tests of significance. Probabilistic inferences can therefore not be drawn from these reported results to any larger population.

Although the results of these studies suggest that contamination of blood samples with isopropyl alcohol may cause a false elevation in the blood glucose concentra-

tion measured with a reflectance photometer, the inadequacies noted above do not allow this causal relationship to be firmly established from the results presented. Even if this kind of false elevation is shown to occur unequivocally, the magnitude of it must be established in order to determine its relevance in clinical decision-making. This has also not been accomplished in a convincing way by any of the studies cited above.

RESEARCH OBJECTIVES

The objectives of this study were to identify if any statistically significant difference existed between the capillary blood glucose concentrations of healthy volunteers tested using a commercially available capillary blood glucose reagent test strip and a reflectance photometer, comparing the results obtained (i) with and without the use of a 70% isopropyl alcohol solution to prepare the site of skin puncture and results obtained (ii) with and without alcohol using the first and second drops of blood.

It was hypothesised that the use of a 70% isopropyl alcohol solution to prepare the site of skin puncture prior to capillary blood sample collection would result in a significantly higher reagent test strip result compared to a similar group of samples collected without alcohol, as measured with a reflectance photometer. It was also hypothesised that significant differences in capillary blood glucose reagent test strip results between samples collected using the first and second drops of blood would be found, independent of the effect of 70% isopropyl alcohol.

METHODS

The study was a prospective, paired, post-test only design utilising self-controls and two factors, namely the use or absence of 70% isopropyl alcohol for skin preparation prior to finger-prick to obtain a capillary blood sample and the use of the first or second drop of capillary blood for reagent strip testing. A convenience sample of 37 healthy volunteers (students from the Department of Emergency Medical Care at the University of Johannesburg) was used after ethical clearance had been obtained from the Faculty of Health Sciences Ethics Committee. Students were invited to participate in the study verbally and those who volunteered were each required to sign a consent form clearly specifying

that they were free to withdraw from the study at any time.

A widely available type of reagent test strip (Haemoglukotest 200-R®, Boehringer Mannheim, Mannheim, Germany) and reflectance photometer (Reflolux®, Boehringer Mannheim, Mannheim, Germany) were used. Each of these devices was calibrated with a calibration strip from each container prior to use with strips from the same container. In addition, each reflectance photometer was calibrated and checked with a control solution to ensure accurate functioning prior to data collection, as outlined in the manufacturer's user manual.

Four capillary blood samples were taken from each subject. The first pair of tests were conducted using the first drop of blood after skin puncture, one with prior preparation of the skin using 70% isopropyl alcohol and one with skin preparation using water. The second pair of tests were conducted in an identical fashion, but using the second drop of blood. Each of the four blood samples referred to above was taken from a separate finger. Wherever alcohol was used to prepare the skin, puncture of the skin and sample collection was initiated before the alcohol had completely evaporated. Blood sample collection and testing was conducted by two third year Emergency Medical Care students who had been assessed in the procedure of capillary blood glucose testing and who had two years of clinical experience in this technique. Universal precautions for the handling of blood and sharp objects were observed throughout blood sample collection and testing.

Data were stored in a backed-up, password-protected electronic spreadsheet application for later analysis (Excel 2003, Microsoft® Corporation). Two-way repeated measures analysis of variance (ANOVA) was carried out using the General Linear Model repeated measures procedure with the two factors being alcohol (two levels – presence or absence of alcohol) and drop of blood used (two levels – first drop and second drop). Differences between groups were considered significant at $P < 0.05$. Statistical analysis was carried out using SPSS® (version 14.0, SPSS Science, Chicago).

RESULTS

Four capillary reagent test strip results were obtained

from each of the 37 subjects. Descriptive data (means, standard deviations and 95% confidence intervals) are shown in Table 1. The mean glucose concentration in the group where the first drop of blood was used with alcohol contamination is the highest. Two-way repeated measures ANOVA did not indicate a significant effect of either factor (alcohol or drop) alone on mean blood glucose concentrations, but a significant interaction between these two factors was demonstrated ($F_{1,36} = 8.41$; $P = 0.006$; see Table 2).

Further analysis of the two interacting factors using one-way ANOVA for the individual factor levels is shown in Table 3. Results indicate that if alcohol is used to prepare the skin prior to a blood glucose reagent strip test being conducted there is a significant difference between results obtained using the first and second drops of blood ($F_{1,36} = 10.29$; $P = 0.003$; Table 3). The mean difference in this case was 0.39 mmol/l. In addition, if the first drop of blood is used for the blood glucose reagent strip test then there is a significant difference between results obtained using alcohol to prepare the skin and not using alcohol to prepare the skin ($F_{1,36} = 8.68$; $P = 0.006$; Table 3). The mean difference between the values in this case was 0.49 mmol/l. An interaction plot for Drop x Alcohol is shown in Figure 1 which graphically depicts the dependence of blood glucose concentration on both factors as described above.

No significant difference existed between results obtained using the first and second drop of capillary blood when alcohol was not used, or between results obtained using the second drop of blood where alcohol was used in one group and not in the other.

DISCUSSION

This study was designed to investigate the relationship between the use of 70% isopropyl alcohol as described above and the blood glucose test strip result, but it also investigated the influence of using the first or second drop of blood for application to the reagent test strip. It was hypothesised that these factors may be related because, theoretically, even if the first drop of blood was contaminated by alcohol on the skin surface, use of the second drop of blood should rectify this.

Table 1: Descriptive data - Capillary blood glucose concentration in four groupings of alcohol and drop factors

Group	n	Mean (mmol/l)	SD	95% CI (mmol/l)
Drop 1 with alcohol	37	3.38	1.28	2.95 – 3.82
Drop 1 without alcohol	37	2.89	1.17	2.49 – 3.28
Drop 2 with alcohol	37	2.99	0.94	2.68 – 3.31
Drop 2 without alcohol	37	3.10	1.40	2.63 – 3.58

Table 2: Two-way repeated measures ANOVA - Comparison of mean capillary blood glucose concentrations within alcohol and drop factors

Source of Variation	df	Sums of Squares	Mean Squares	F	P
Alcohol	1	1.27	1.27	2.62	0.114
Error (Alcohol)	36	17.42	0.48	-	-
Drop	1	0.10	0.10	0.40	0.532
Error (Drop)	36	9.29	0.26	-	-
Alcohol x Drop	1	3.30	3.30	8.41	0.006
Error (Alcohol x Drop)	36	14.13	0.39	-	-

Two previous reports in the scientific literature of erroneous results obtained from blood glucose reagent strips when alcohol is used for skin preparation have found differences between blood glucose concentrations with and without alcohol contamination ranging from 0.1 mmol/l to 10.6 mmol/l (Phillips *et al.* 1977:790; Grazaitis & Sexson, 1980:222). As revealed above, both of these studies were methodologically flawed. The 100-fold range in alcohol-induced blood glucose elevation identified in the two studies supports the notion that this problem required reassessment with a more robust methodology and statistical analysis. This study has provided such a reassessment and has revealed a significant interaction between the use of 70% isopro-

pyl alcohol for skin preparation and the choice of first or second drop of blood to be applied to the reagent test strip. Most notably, when alcohol was used for preparation of the capillary blood sampling site and the first drop of blood was chosen for application to the reagent test strip without the evaporation of the alcohol before skin puncture, a significant elevation of 0.49 mmol/l in mean blood glucose concentration as measured with a reflectance photometer resulted.

Two important qualifiers must be added to this finding. Firstly, this effect could be avoided by choosing the second drop of blood for application to the reagent test strip, as recommended by the manufacturer of the test

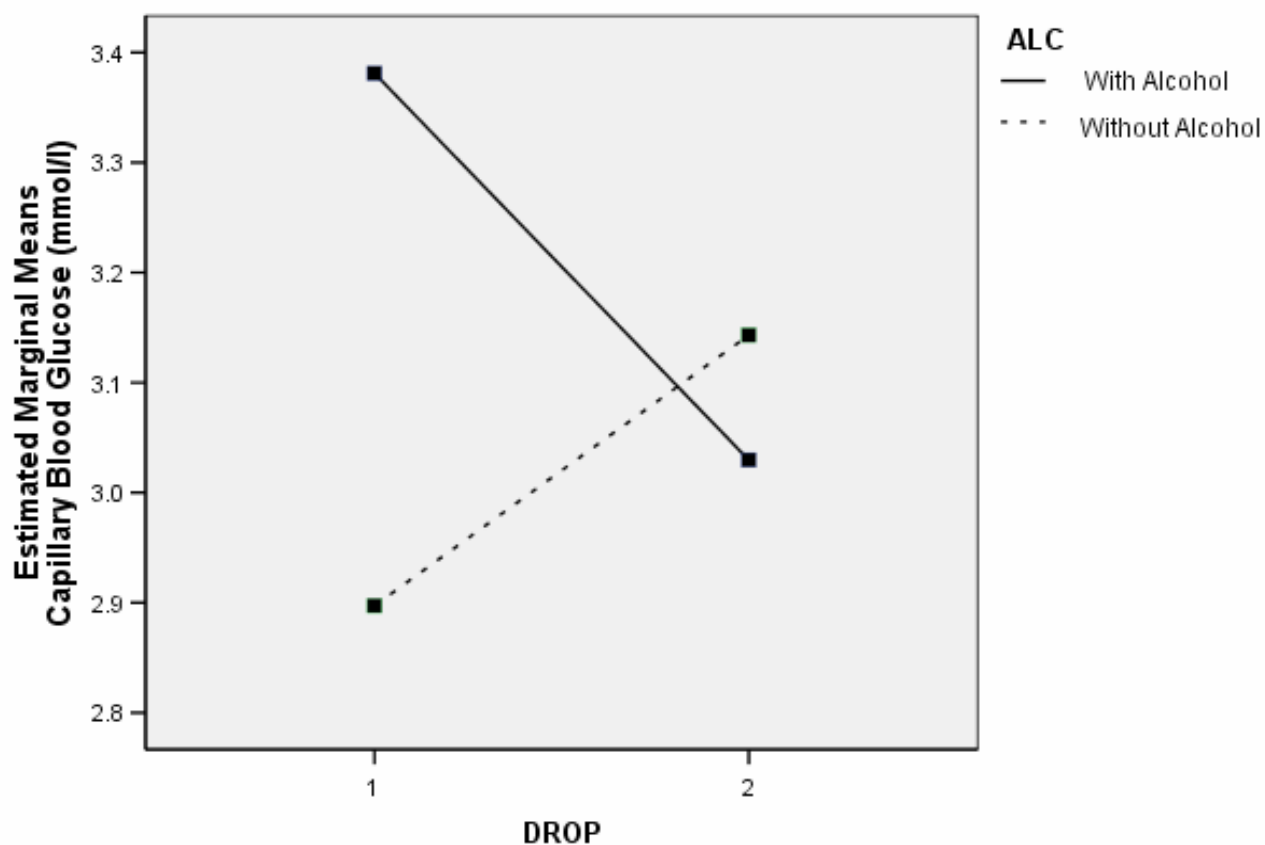


Figure 1: Interaction plot of drop and alcohol factors

Table 3: One-way repeated measures ANOVA for individual factor levels of alcohol and drop factors

Source of Variation	df	Sums of Squares	Mean Squares	F	P
Factor Level - First Drop of Blood					
With Alcohol	1	2.28	2.28	8.68	0.006
Error (With Alcohol)	36	9.48	0.26	-	-
Without Alcohol	1	1.12	1.12	2.89	0.098
Error (Without Alcohol)	36	13.95	0.39	-	-
Factor Level - With Alcohol					
First Drop	1	4.33	4.33	10.29	0.003
Error (First Drop)	36	15.16	0.42	-	-
Second Drop	1	0.24	0.24	0.52	0.474
Error (Second Drop)	36	16.40	0.46	-	-

strips used in this study. Doing so in this study resulted in a significant lowering of mean blood glucose concentration almost equal in magnitude to the elevation in blood glucose concentration detected between the alcohol and no alcohol groups where the first drop of blood was chosen (0.49 and 0.39 mmol/l respectively). Secondly, even if the first drop of blood is applied to the reagent test strip as described above, the elevation in blood glucose concentration caused by the use of alcohol in this study was small (0.49 mmol/l). Although this is statistically significant given the sample size and variance in each factor grouping, it is highly unlikely that such a small elevation would be clinically significant. In a clinical setting, a false elevation in blood glucose concentration of roughly 0.5 mmol/l should not mask a dangerously large deviation below any commonly used minimum threshold for blood glucose concentration and thus should not result in supplemental glucose being withheld from any patient who urgently requires this form of treatment.

In principle, the results of previous studies suggesting that contamination of capillary blood samples with 70% isopropyl alcohol causes a false elevation of blood glucose concentration are supported by this study. However the magnitude of false elevation in blood glucose concentration caused by this effect as reported by Grazitis and Sexson (1980:222) appears to be a gross overestimation at roughly twenty times that documented in this study.

LIMITATIONS OF THE STUDY

Although the biochemical basis for most capillary blood glucose reagent test strips is similar, the results and conclusions of this study can only be stated with certainty in relation to the specific products used to gather the data (Haemo-glukotest 200-R® reagent test strip and Reflolux® reflectance photometer, Boehringer Mannheim). In addition, the sample of volunteers was not truly random, although there was nothing intentionally systematic in the way the sample was drawn.

CONCLUSION

The use of 70% isopropyl alcohol to prepare the site of skin puncture prior to capillary blood sampling for a blood glucose reagent strip test using a reflectance

photometer results in a blood glucose elevation of approximately 0.49 mmol/l compared to blood glucose concentrations from samples obtained without the use of isopropyl alcohol. This effect is seen when the first drop of blood after skin puncture is applied to the reagent test strip. If 70% isopropyl alcohol is used as described above, but the first drop of blood is removed and a second drop of capillary blood is placed on the reagent test strip, a decrease in blood glucose concentration of approximately 0.39 mmol/l is seen compared to the concentration obtained if the first drop of capillary blood is used. Although these differences are statistically significant it is unlikely that a false elevation in blood glucose concentration of this magnitude caused by 70% isopropyl alcohol will result in supplemental glucose being withheld from any patient who is profoundly hypoglycaemic.

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