J Anesth (1996) 10:140–143

Journal of
Anesthesia

Experimental study of efficacy and optimal dose of intraoperative glucose in rabbits under general anesthesia

HIDEKI KAMURO[1], HIDETO KODAIRA[1], SHUN-ICHI ABE[1] and RYO OGAWA[2]

[1] Research Division, The Green Cross Corporation, 2-25-1 Shodai-Ohtani, Hirakata, Osaka 573, Japan
[2] Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113, Japan

Abstract: This experimental study was designed to investigate the efficacy of glucose loading during surgery. Rabbits, fasted overnight, received 20 ml·kg^{-1}·h^{-1} fluid infusion containing glucose at various concentrations (0, 0.5, 1.0, 1.5, 2.0 %w/v) for 3 h intraoperatively. Plasma glucose level increased after the beginning of operation, but the increase was slight in groups given 0.2 g·kg^{-1}·h^{-1} or lower doses of glucose. Glucose at higher doses caused marked hyperglycemia. These higher doses also promoted urinary glucose excretion, and in the group given the maximum glucose dose (0.4 g·kg^{-1}·h^{-1}), this parameter was significantly elevated compared with findings in the 0.2 g·kg^{-1}·h^{-1} group ($P < 0.05$), whereas it showed no significant difference among groups given 0–0.2 g·kg^{-1}·h^{-1}. The liver glycogen content in animals that received no glucose was significantly lower than that of the 0.2 g·kg^{-1}·h^{-1} group ($P < 0.01$). However, there was no correlation between glycogen level and glucose dose among groups receiving glucose. These results suggest that intraoperative glucose supplementation is effective in preventing glycogen depletion, and indicate that, to avoid glucose overloading, the optimal dose is 0.1–0.2 g·kg^{-1}·h^{-1}.

Key words: Intraoperative fluid infusion, Glucose, Plasma glucose, Glucose excretion, Glycogen

Introduction

In clinical practice, glucose infusions are commonly used to provide energy [1–3], to prevent ketosis and hypoglycemia, and to conserve protein. Many patients are able to receive glucose as an energy supply substrate perioperatively, since the patient is obliged to fast overnight or longer before most operations [4]. However, there is no universal agreement as to the optimal infusion rate and amount of glucose required for intraoperative use.

With the aim of contributing to the resolution of this question, we investigated experimentally the optimal glucose dose in intraoperative fluid infusion during a surgical procedure carried out in rabbits subjected to general anesthesia.

Materials and methods

This study was undertaken with male Japanese white rabbits weighing between 2.45 and 2.84 kg (aged about 3 months). The animals were fasted overnight before undergoing general anesthesia for surgical procedures lasting 3 h.

The rabbits were randomly assigned to five groups, of eight animals each. They were anesthetized with sodium pentobarbital (30 mg·kg^{-1}, iv) and anesthesia was maintained with 60% nitrous oxide in oxygen and 0.5% sevoflurane under artificial respiration. A polyvinyl chloride cannula (φ 1.5 mm) was then inserted in the femoral artery and laparotomy was performed. The small intestine, intestinum cecum, and attached tissues, such as the mesenterium, were removed from the abdomen, subjected to stimulation by handling, and exposed to room air for 3 h. Fluid infusion was performed throughout the operation at a constant flow rate of 20 ml·kg^{-1}·h^{-1} with an intravenous drip injection of Ringer's acetate solution without glucose or containing 0.5, 1.0, 1.5, or 2.0 %w/v of glucose, which concentrations correspond to 0, 0.1, 0.2, 0.3, and 0.4 g·kg^{-1}·h^{-1}. The composition of the infusions is shown in Table 1.

Two milliliters of arterial blood was withdrawn from the femoral artery into a heparinized syringe immediately before the beginning of the infusion, and at the middle and end of the infusion. Plasma was obtained by centrifugation (3000 rpm for 15 min) and frozen (−20°C) until analysis was performed. Immediately

Address correspondence to: H. Kamuro
Received for publication on September 13, 1995; accepted on January 31, 1996

Table 1. Composition of infusion

Ingredient	
Electrolytes (mEq·l^{-1})	
Na^+	140
K^+	4
Mg^{2+}	2
Ca^{2+}	3
Cl^-	115
Acetate	25
Gluconate	3
Citrate	6
Glucose (%w/v)	0, 0.5, 1.0, 1.5, 2.0

after infusion, a liver specimen was obtained from each rabbit for the measurement of glycogen content. A cannula was inserted in the bladder to collect all urine during infusion, and urinary glucose concentration was measured and glucose excretion calculated.

Plasma and urinary glucose were measured enzymatically by the glucose-oxidase method, using a commercially available kit (Glucose B-Test: Wako Pure Chemical Co, Tokyo, Japan; CV less than 2.5%). Liver glycogen was determined by a previously described method [5,6]. Frozen liver samples, or purified glycogen (Wako Pure Chemical Co, Tokyo, Japan) as a standard, were solubilized with 30% (w/v) KOH by boiling at 100°C for 30 min. Glycogen was precipitated by the addition of 99% ethanol and hydrolyzed by 2N H_2SO_4 in a boiling water bath for 2 h. After neutralization was carried out with 2N NaOH, the amount of glycogen was calculated from the glucose value determined in the hydrolyzed glycogen sample, using the method cited above.

All values are expressed as means ± SD. Statistical significance was assessed by performing analysis of variance (one-way ANOVA) and multiple comparison (Tukey-Kramer) tests between all groups. However, for simplicity, significance relative to the 0.2 g·kg^{-1}·h^{-1} group only was considered. Probability values of less than 0.05 were considered significant.

Results

Figure 1 shows the time course of changes in plasma glucose values. Plasma glucose concentrations rose after the beginning of operation and infusion, but the increases were slight in the groups given 0.2 g·kg^{-1}·h^{-1} of glucose or less. On the other hand, glucose at more than 0.2 g·kg^{-1}·h^{-1} caused marked hyperglycemia, the differences being significant compared with the 0.2 g·kg^{-1}·h^{-1} group ($P < 0.05$ or $P < 0.01$).

Figure 2 shows the urinary excretion of glucose. This excretion was negligible in groups receiving glucose at

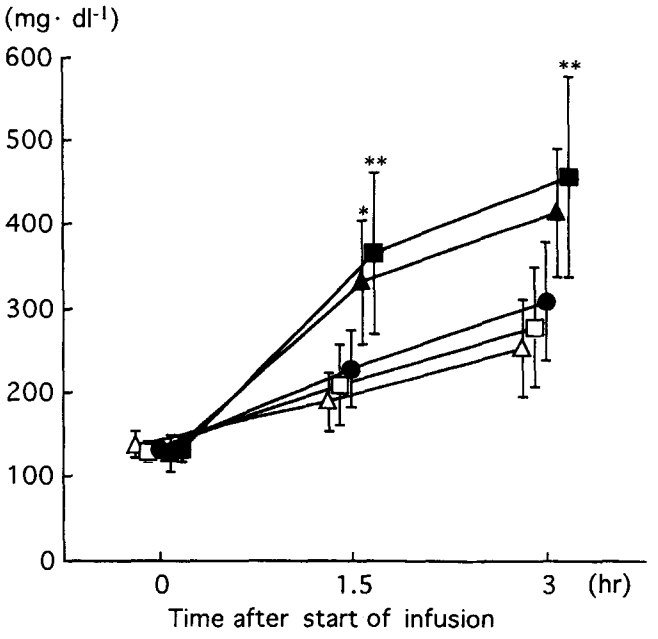

Fig. 1. Time course of changes in plasma glucose concentrations. *Open triangles*, 0% (0 g·kg^{-1}·h^{-1}) group; *open squares*, 0.5% (0.1 g·kg^{-1}·h^{-1}) group; *closed circles*, 1.0% (0.2 g·kg^{-1}·h^{-1}) group; *closed triangles*, 1.5% (0.3 g·kg^{-1}·h^{-1}) group; *closed squares*, 2.0% (0.4 g·kg^{-1}·h^{-1}) group. *$P < 0.05$; **$P < 0.01$, significantly different from 1.0% group

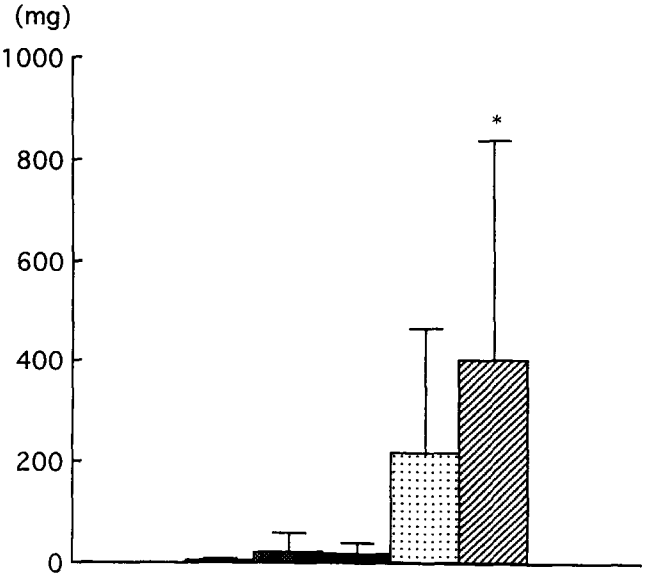

Fig. 2. Urinary excretion of glucose during infusion. *Open bar*, 0% (0 g·kg^{-1}·h^{-1}) group; *shaded bar*, 0.5% (0.1 g·kg^{-1}·h^{-1}) group; *solid bar*, 1.0% (0.2 g·kg^{-1}·h^{-1}) group; *dotted bar*, 1.5% (0.3 g·kg^{-1}·h^{-1}) group; *hatched bar*, 2.0% (0.4 g·kg^{-1}·h^{-1}) group. *$P < 0.05$, significantly different from 1.0% group

0.2 g·kg^{-1}·h^{-1} or less. However, increased excretion was frequently noted in the groups given 0.3 and 0.4 g·kg^{-1}·h^{-1} of glucose (217.7 ± 246.9 and 400.5 ± 439.6 mg, respectively), the value in the latter group

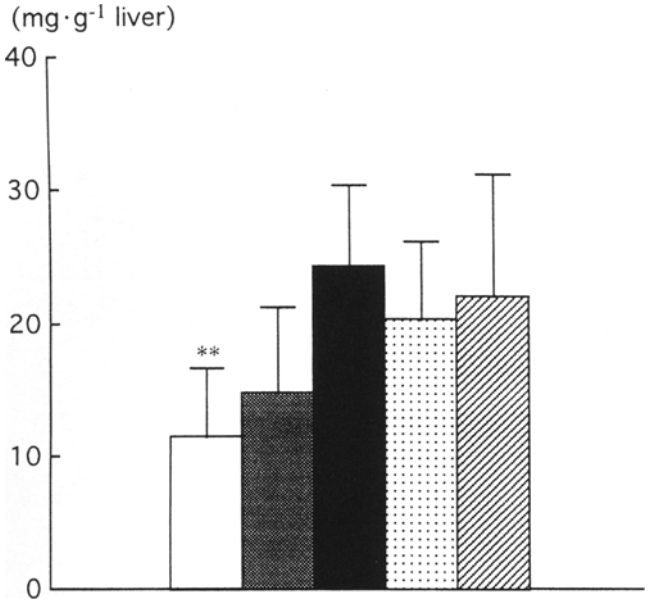

Fig. 3. Glycogen content in liver immediately after infusion. *Open bar*, 0% (0 g·kg^{-1}·h^{-1}) group; *shaded bar*, 0.5% (0.1 g·kg^{-1}·h^{-1}) group; *solid bar*, 1.0% (0.2 g·kg^{-1}·h^{-1}) group; *dotted bar*, 1.5% (0.3 g·kg^{-1}·h^{-1}) group; *hatched bar*, 2.0% (0.4 g·kg^{-1}·h^{-1}) group. $^{**}P < 0.01$, significantly different from 1.0% group

being significantly different from that for the 0.2 g·kg^{-1}·h^{-1} group ($P < 0.05$). Glucose excretion ratios (percentage of administered dose) in the groups that received 0.1–0.4 g·kg^{-1}·h^{-1} of glucose were 2.8 ± 4.9, 0.9 ± 1.6, 9.2 ± 10.5, and 12.8 ± 14.3%, respectively.

Figure 3 shows glycogen content in the liver. It was low compared to the amount of glycogen in the liver of fed rabbits (about 40 mg·g^{-1} or more; data not shown), for which the most likely explanation is the overnight fasting. The glycogen content of animals that received no glucose was markedly decreased compared to the groups given glucose, and was significantly lower—by about 50%—than that of animals given 0.2 g·kg^{-1}·h^{-1} glucose ($P < 0.01$). However, no further increases in glycogen content in the liver were associated with the administration of more than 0.2 g·kg^{-1}·h^{-1} glucose.

Discussion

Surgical stress is associated with the activation of the sympathetic nervous system, whereby so-called surgical diabetes occurs. The surgical stress in this experiment was taken to be of medium degree or more, since, in laboratory animals, exposure of the small intestine for 3 min, accompanied by manipulation, is designated medium-degree surgical stress, corresponding to the stress of gastrectomy [7].

Because of this surgical stress, elevated plasma glucose levels were observed even in animals in which infusion of a fluid not containing glucose was performed. Moreover, notwithstanding glucose loading, the increase of plasma glucose was not enhanced in groups receiving glucose at the rate of 0.1 or 0.2 g·kg^{-1}·h^{-1} compared with infusion without glucose. Ogawa et al. [8] and Tabo et al. [9] also reported that glucose administration, at the rate of 0.25 g·kg^{-1}·h^{-1}, as a link in intraoperative fluid therapy, did not cause an extra rise in blood sugar and was an efficient energy supply. Kuze et al. [10] found that Ringer's solution containing glucose, especially given in large amounts, seemed to affect the metabolism, and they recommended that the dose and the infusion rate should be adjusted to avoid metabolic changes. The results of the present study indicate that if the administration rate is 0.2 g·kg^{-1}·h^{-1} or less, glucose may be given during major surgery without the risk of overload.

The urinary excretion of glucose was closely related to the development of hyperglycemia, this phenomenon being negligible in the groups given glucose at the rate of 0.2 g·kg^{-1}·h^{-1} or less. This result agrees with that of Kawachino and colleagues [11], who reported that, in subjects given 0.25 g·kg^{-1}·h^{-1} of glucose intraoperatively, the urinary excretion of glucose was negligible (0.06% of administered dose) by 4 h after infusion. However, a glucose load of more than 0.2 g·kg^{-1}·h^{-1} raised glucose excretion in urine. These results and the findings noted in the foregoing paragraph indicate that, during surgery, the utilization of glucose is decreased and the tolerance limit of glucose infusion is reduced, whereas the capacity of glucose metabolism is generally held to be up to 0.5 g·kg^{-1}·h^{-1} of intravenous injection [9]. Accordingly, to avoid hyperglycemia and the excessive urinary excretion of glucose during surgical procedures, the glucose dose should be 0.2 g·kg^{-1}·h^{-1} or less.

Perioperative infusion without glucose was disadvantageous for the protection of liver glycogen. The suppression of glycogen depletion seen with glucose administration may be the result of an increase in the precursor substrate required for glycogen synthesis, since hepatocytes can obtain glucose independently of the action of insulin by passive transport [12]. Surprisingly, however, the highest and second highest doses of glucose we employed did not exert a stronger protective effect than the middle dose. It is assumed that, at the higher doses, increased levels of the precursor substrate actually exceeded the glycogenesis capacity of the enzyme. Thus, glucose loading exceeding 0.2 g·kg^{-1}·h^{-1} is not effective in preventing the decrease of liver glycogen. Since the level of glycogen storage in the liver ordinarily depends on the time lapse since the last meal, it was difficult to establish a single value as standard. In our preliminary study, the amount of glycogen in the

liver of non-fasted rabbits was about 40 mg·g^{-1}, but this value could not necessarily be taken as the saturation point, since the liver specimen was obtained in the afternoon when appetite was likely to have been low. The standard value for liver glycogen in the fed condition was therefore assessed as 40 mg·g^{-1} or more.

In normal rabbits, the tolerance limit for intravenous glucose infusion is less than 0.85 g·kg^{-1}·h^{-1}, and this virtually agrees with the value in humans [13]. Consequently, if the results of this experimental study were to be extrapolated to the clinical setting, the optimal dose of glucose during surgery would be 0.1–0.2 g·kg^{-1}·h^{-1}. Furthermore, since patients commonly receive intraoperative fluid at the rate of 10–20 ml·kg^{-1}·h^{-1} [8], we suggest that the ideal concentration of glucose in extracellular fluid replacement is 1%.

Kimura et al. [14,15] found that lactated Ringer's solution with high potassium levels was effective in suppressing increases in serum glucose during surgery, since the high dose of potassium led to a concomitant intracellular influx of potassium and glucose. Therefore, the optimal dose of glucose may change in response to the dose of potassium infused simultaneously, and our results and recommendations must be limited to cases in which the conventional concentration of potassium (4 mEq/l) is present in the extracellular fluid replacer.

In conclusion, we have shown that intraoperative glucose supplementation in rabbits is effective in suppressing liver glycogen depletion. To avoid glucose overloading, the optimal intraoperative dose is 0.1–0.2 g·kg^{-1}·h^{-1} at a fluid infusion rate of 20 ml·kg^{-1}·h^{-1}.

References

1. Liaw KY, Askanazi J, Michelsen CB, Furst PF, Elwyn DH, Kinney JM (1982) Effect of postoperative nutrition on muscle high energy phosphate. Ann Surg 195:12–18
2. Hagerdal M, Caldwell CB, Gross JB (1983) Intraoperative fluid management influences carbon dioxide production and respiratory quotient. Anesthesiology 59:48–50
3. Kondo U, Ogata M, Shigematsu A (1990) The effect of glucose loading on changes of ketone and glucose metabolism during gastrectomy (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 39:465–472
4. Sieber FE, Smith DS, Traystman RJ, Wollman H (1987) Glucose: A reevaluation of its intraoperative use. Anesthesiology 67:72–81
5. Hassid WZ, Abraham S (1957) Chemical procedures for analysis of polysaccharides. In: Colowick SP, Kaplan NO (eds) Methods in enzymology III. Academic, New York, pp 34–50
6. Passonneau JV, Lauderdale VR (1974) A comparison of three methods of glycogen measurement in tissues. Anal Biochem 60:405–412
7. Sano K (1986) An experimental study of various energy sources in total parenteral nutrition (in Japanese with English abstract). Geka to Taisha, Eiyo (Jpn J Surg Metab and Nutr) 20:96–111
8. Ogawa R, Kunimoto F, Gohshi Y, Hasegawa S (1987) Comparison of lactated Ringer's and 5% dextrose-saline mixture solutions as intra-operative hydrating agents (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 36:94–100
9. Tabo E, Ookuma Y, Amakawa K, Takasaki Y, Kimura S, Arai T (1993) Change of blood glucose under general anesthesia—Effects of glucose concentration in pre- or perioperative fluid infusion (in Japanese). Rinsho Masui (Jpn J Clin Anesth) 17:1313–1316
10. Kuze S, Naruse T, Ito Y, Nakamaru K (1990) Comparative study of intravenous administration of Ringer's lactate, Ringer's acetate and 5% glucose containing these Ringer's solutions in human beings. J Anesth 4:155–161
11. Kawachino N, Sato K, Aono K (1981) Carbohydrate infusion during surgery (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 30:1091–1098
12. Tominaga S, Kubota T, Hiratsuka M, Nakajima T, Himuro H, Aono K (1992) Study on the composition of a solution for intraoperative infusion in minor oral surgery (in Japanese with English abstract). Nihon Shika Masui Gakkai Zasshi (Jpn J Dent Anesth Soc) 20:442–452
13. Robert PG (1960) Parenteral nutrition. Physiol Rev 40:150–186
14. Kimura K, Endou E, Fukui A, Takaori M (1991) Intraoperative fluid therapy by lactated Ringer's solution with various concentrations of potassium (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 40:42–48
15. Kimura K, Fukui A, Endou E, Takaori M (1991) Changes in blood sugar levels following infusion of lactated Ringer's solution with various concentrations of potassium and glucose (in Japanese with English abstract). Masui (Jpn J Anesthesiol) 40:1454–1460