Effect of General Anesthesia on
Plasma Ascorbic Acid Level

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ABSTRACT

Ascorbic acid (AsA) and dehydroascorbic acid (DHA) in plasma, and the total vita-
min C (AsA + DHA) in urine after oral surgery were measured to investigate whether
general anesthesia has effects on the level of plasma AsA. Plasma AsA decreased sig-
nificantly on the 1st and 3rd post-operative day in the general anesthesia group, but
not in the local anesthesia group. A decrease in the AsA level was seen in both the
halothane group and the neuroleptanesthesia group. Plasma DHA was not detected
pre-operatively, but increased post-operatively and the total vitamin C in the urine
decreased on the 1st post-operative day in the general anesthesia group.

It was concluded that general anesthesia caused a decrease in the plasma AsA level.
This can be only partially explained by the oxidation of AsA.

We are going to investigate other causes as the degree of decrease of AsA was larger
than the degree of increase of DHA.

Ascorbic acid (AsA) is a co-factor in the
hydroxylation of proline in the synthesis of col-
lagen and plays an important role in the wound
healing process in which collagen synthesis is ac-
celerated. It has been reported that plasma AsA
decreases in the post-operative period as a result
of consumption by the synthesis of collagen
which is necessary for wound healing[14]. It also
has been reported that tissue AsA levels are
decreased in rats after exposure to physical
stresses[1]. It has become apparent that AsA is
an important factor in xenobiotic metabolism[17].
Collagen synthesis and metabolism and the ex-
cretion of various drugs administered during sur-
gery are accelerated in the post-operative period.
Since the decrease of AsA is disadvantageous
to the human body, it is important to investigate
the mechanism of this phenomenon. It is not
clear whether general anesthesia is related to
the decrease of AsA in plasma. The purpose of

this study is to investigate the effect of gener-
al anesthesia on the level of plasma AsA. We
measured the level of plasma AsA and compared
the values in cases of general anesthesia with
those in cases of local anesthesia, separating out
the values in the cases receiving halothane from
those in the cases receiving neuroleptanesthesia.
We also measured the plasma dehydroascorbic
acid (DHA) and the total vitamin C in the urine
to evaluate the cause of the decrease in plasma
AsA in the post-operative period.

SUBJECTS AND METHODS

The subjects were composed of 38 patients (23
men and 15 women) who underwent oral sur-
gery. They were classified into a general
anesthesia group and a local anesthesia group.
The former was further classified into a
halothane group (GOF) and neuroleptanesthesia
group (NLA). The patients of GOF group were

anesthetized with thiopental (4-5mg/kg) and halothane, and the trachea was intubated after a 4mg does of pancuronium. Anesthesia was maintained with halothane and nitrous oxide in oxygen. The patients of NLA group were anesthetized with droperidol (5mg), fentanyl (0.2-0.3mg) and thiopental (3-4 mg/kg), and the trachea was intubated after a 4mg does of pancuronium. Anesthesia was maintained with fentanyl and nitrous oxide in oxygen.

Blood samples were obtained after an overnight fast on the pre-operative, and the 1st, 3rd and 7th post-operative day. Urine was collected continuously after the induction of anesthesia and 21hr or 24hr specimens were obtained on the appropriate post-operative days.

The AsA and DHA in plasma were measured by Okamura's method[9]. The total vitamin C in the urine was also measured by Okamura's method[10]. The pre-operative and post-operative values of the plasma AsA were compared using a Student's t-test.

RESULTS

Table 1 shows the diagnoses of the 38 patients for whom the plasma AsA level was determined. The plasma AsA levels decreased significantly on the 1st and 3rd post-operative day in the general anesthesia group, but not in the local anesthesia group (Table 2). The mean value of the amount of blood loss was 52 ± 18g in the general anesthesia group and 41 ± 18g in the local anesthesia group, which is not a significant difference. Table 3 shows the level of the plas-

Table 1. Diagnoses of the 38 patients whose plasma were used to measure ascorbic acid

General anesthesia		Local anesthesia	
Fracture	6	Cyst	12
Benign tumor	6		
Sialolithiasis	4		
Cyst	4		
Malignant tumor	2		
Progenia	2		
Others	2		
Total	26	Total	12

Table 2. Plasma ascorbic acid levels in patients receiving general anesthesia or local anesthesia

	Pre-operation	Post-operative days		
		1	3	7
General anesthesia (mg/dl)	1.02 ± 0.31 0.99 ± 0.31 1.24 ± 0.15	(n = 11) 0.79 ± 0.22****	(n = 10) 0.75 ± 0.17****	(n = 5) 0.97 ± 0.31
Local anesthesia (mg/dl)	0.99 ± 0.30 0.84 ± 0.12	(n = 11) 0.95 ± 0.43	(n = 4) 0.71 ± 0.08	

The values are mean ± SD. **** Significantly different from pre-operative values, $p < 0.005$.

Table 3. Plasma ascorbic acid levels in patients receiving halothane(GOF) or neuroleptics(NLA) for general anesthesia

	Pre-operation	Post-operative days		
		1	3	7
GOF (mg/dl)	0.92 ± 0.28 0.87 ± 0.27 0.96 ± 0.33	(n = 14) 0.73 ± 0.23****	(n = 11) 0.72 ± 0.19**	(n = 4) 0.71 ± 0.28
NLA (mg/dl)	1.02 ± 0.36 0.96 ± 0.34 1.12 ± 0.24	(n = 9) 0.72 ± 0.34***	(n = 9) 0.70 ± 0.30*	(n = 5) 0.88 ± 0.42

The values are mean ± SD.
  * Significantly different from pre-operative values, $p < 0.05$.
 ** Significantly different from pre-operative values, $p < 0.02$.
*** Significantly different from pre-operative values, $p < 0.01$.
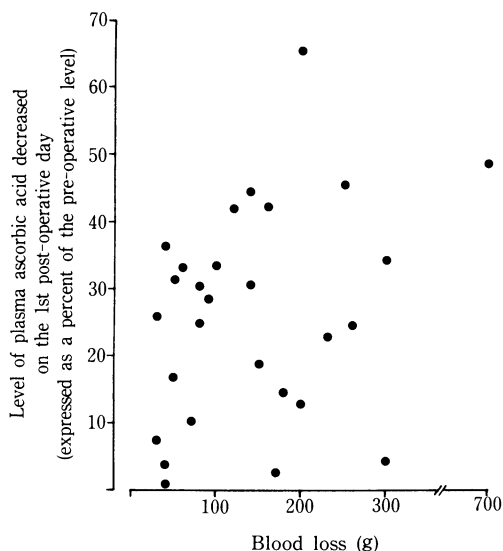**** Significantly different from pre-operative values, $p < 0.005$.

Fig. 1. The relationship between the volume of blood loss and the level of plasma AsA decreased on the 1st post-operative day for the 28 patients who underwent general anesthesia. The decreased plasma level of AsA is expressed as a percentage of the preoperative level. The correlation coefficient was 0.317. The correlation was not seen.

Table 4. Plasma dehydroascorbic acid level (μg/ml)

Pre-operation	Post-operative days		
	1 (n = 12)	3 (n = 13)	7 (n = 7)
N.D.	8.3 ± 9.4	16.2 ± 14.5	2.9 ± 7.6

The values are mean ± SD. N.D.: Not Detectable

Table 5. Urine volume and urinary total vitamin C level per hour

		Post-operative days	
		1 (n = 7)	2 (n = 5)
Urine volume	(%)	58 ± 41	115 ± 79
Total vitamin C	(%)	49 ± 33	93 ± 52

The values are mean ± SD and expressed as a percent of the value obtained on the day of surgery.

ma AsA separated out by the type of general anesthesia (GOF or NLA). No difference between the GOF group and the NLA group was seen. Fig. 1 shows the relationship between the amount of blood loss and the level of plasma AsA decreased on the 1st post-operative day, expressed as a percent of the pre-operative value. No correlation was seen. Table 4 shows the lev-

els of the plasma DHA, which could not be detected pre-operatively but increased most significantly on the 3rd post-operative day. Table 5 shows the urine volumes and total vitamin C levels as a percent of the values on the day of surgery. Both parameters decreased slightly on the 1st post-operative day, but rose on the 2nd post-operative day to the value on the day of surgery, or above.

DISCUSSION

It has become apparent that AsA has several physiological actions in addition to its role as an essential co-factor of collagen biosynthesis. In particular, the relationship between AsA and the metabolism of xenobiotics has been studied. Wagstaff et al[16] suggested that guinea pigs required more than 200 ppm of AsA in order for Dieldrin to induce O-demethylase and aniline oxidase activity in the liver microsomes. The minimum dietary level of AsA recommended by the National Research Council is 200 ppm. Kato et al[7] demonstrated that the inhibition of the increase in body weight produced by the intake of 50 ppm of polychlorinated biphenyl was partially overcome by the intake of 2000 ppm of AsA which is 10 times as much as the usual requirement. These two studies indicate that the intake of megadoses of AsA maintain normal biological reactions and decrease the toxicity of xenobiotics, and support the usefulness of administration of AsA in high doses.

The effect of general anesthetics on the level of AsA *in vivo* has not been previously reported in detail. Irvin et al[5] reported that there was no correlation between the decrease of AsA in leucocytes and the degree of surgical stress. There was also no correlation between the volume of blood loss, which reflects the degree of surgical stress, and the decrease of plasma AsA in this study. This implies that the decrease in plasma AsA can not be explained by the consumption of AsA in collagen synthesis in the surgical wound. The plasma AsA decreased significantly in the cases receiving general anesthesia, but not in the cases receiving local anesthesia. From these findings, it may be concluded that the plasma AsA is decreased by general anesthesia. The stress of general anesthesia probably affected the level of the plasma AsA because no difference was seen be-

tween the values of the GOF and NLA groups. Although not detected pre-operatively, DHA increased most significantly on the 3rd post-operative day. We must keep in mind the toxicity of DHA because it is thought to cause diabetes[11] and neurological disturbances[15]. However, the DHA almost returned to normal by the 7th day and no clinical problems attributable to DHA were seen in this study.

Arai[1] reported that she exposed rats to various stresses such as forced muscular exercise, cold and X-ray irradiation, and measured the level of AsA in the liver, kidney and adrenal glands. These stresses caused a significant decrease of AsA in these organs and a slight increase of DHA. Reduced glutathione (GSH) was also decreased in the liver and blood by these stresses. As GSH had been reported to reduce DHA[2], she presumed that the decrease of GSH induced the increase of DHA in the plasma. The decrease could be only partially explained by the oxidation of AsA because the increase of DHA was very slight. As GSH in organs decreases in response to stress, DHA might increase.

It is impossible to explain the decrease in the plasma AsA by the excretion of AsA in urine because the total vitamin C in urine had a tendency to decrease on the 1st post-operative day, and it is thought that the excretion of AsA in urine depends on the plasma concentration[4]. In addition, it is unlikely that the plasma AsA decreases by being transferred to other organs because the tissue level of AsA decreases under stress as reported by Arai[1]. Loh[8] reported that the level of AsA in leucocytes reflects the level of that in organs, and the level of AsA in plasma reflects the rate of metabolic turnover. It is most likely that the AsA was metabolized and decomposed. We are planning animal experiments to elucidate this mechanism.

Suitable doses and routes of post-operative AsA administration have not been established. It has been suggested that the administration of AsA is useful in the post-operative period, especially in cases undergoing general anesthesia, because the plasma AsA is significantly decreased in such patients. But the administration of excess doses of AsA has disadvantages as well. AsA promotes lipid peroxidation in the liver mitochondria[13] and the brain[12] and can induce hemolysis[6]. However, Chen[3] reported that

vitamin E prevents both the lipid peroxidation in the liver and hemolysis. Therefore, the administration of AsA in the post-operative period, possibly with vitamin E as well, may have therapeutic benefit.

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