Tohoku J. Exp. Med., 2008, **214**, 327-332

Olfactory Stimulation Using Black Pepper Oil Facilitates Oral Feeding in Pediatric Patients Receiving Long-Term Enteral Nutrition

Mitsutoshi Munakata,[1, 3] Kaori Kobayashi,[2] Junko Niisato-Nezu,[1] Souichiro Tanaka,[1] Yosuke Kakisaka,[1, 3] Takae Ebihara,[4] Satoru Ebihara,[4] Kazuhiro Haginoya,[1] Shigeru Tsuchiya[3] and Akira Onuma[1]

[1]Division of Pediatric Neurology, Takuto Rehabilitation Center for Children, Sendai, Japan
[2]Division of Rehabilitation, Takuto Rehabilitation Center for Children, Sendai, Japan
[3]Department of Pediatrics, Tohoku University School of Medicine, Sendai, Japan
[4]Department of Geriatrics and Gerontology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Patients with severe neurological disorders often require enteral nutrition (EN). Since long-term EN can cause multiple complications, reinstating the oral intake of food is beneficial. Olfactory stimulation using black pepper oil (BPO), a strong appetite stimulant, was reported to facilitate swallowing in older people. Therefore, the effects of olfactory stimulation with BPO were investigated in pediatric patients receiving long-term EN due to neurological disorders. The effects of scenting with BPO for 1 min immediately before every meal were evaluated in ten patients: 4 boys and 6 girls, aged 19-97 months (51 ± 26 months). The neurological disorders included periventricular leukomalacia (3 patients), hypoxic ischemic encephalopathy (3), Costello syndrome (1), Russell-Silver syndrome (1), Miller-Dieker syndrome (1), and cerebral palsy of unknown etiology (1). In eight of these patients, BPO intervention was continued for 3 months. Five of these eight patients showed increases in the amount of oral intake with desirable effects including facilitated swallowing movement, although complete elimination of the need for EN was not achieved. In the other three patients, BPO intervention was not effective; severe cerebral tissue loss, profound malformation or intractable seizures seemed to reduce the efficacy of BPO. In two cases, BPO intervention was discontinued due to cough or because the odor of BPO was unbearable to the family. In conclusion, olfactory stimulation with BPO facilitated oral intake in a subset of patients on long-term EN. BPO stimulation may be useful for facilitating oral intake when used in combination with conventional methods. ————— dysphagia; food aversion; enteral nutrition; black pepper oil; cerebral palsy.
Tohoku J. Exp. Med., 2008, **214** (4), 327-332.

Received December 31, 2007; revision accepted for publication February 18, 2008.
Correspondence: Mitsutoshi Munakata, M.D., Ph.D., Department of Pediatrics, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
e-mail: m-munakata@umin.ac.jp

Patients with severe neurological disorders often have problems with the oral intake of food and require the use of enteral nutrition (EN). Although EN ensures that daily nutritional requirements are met, multiple complications have been reported with long-term EN, including unexpected micronutrient deficiencies, altered gastrointestinal tract function, and reduced psychosocial stimulation (Kumode 2003; Sleigh et al. 2004; Munakata et al. 2006). Therefore, reinstating oral intake is highly beneficial even if it supplies only part of the patient's nutritional requirements. However, the introduction of oral intake is often difficult in patients receiving long-term EN as background diseases can often affect aspects of the eating process, such as appetite, perception of food, and swallowing (Ohrui 2005). In addition, children who are deprived of oral feeding experiences during developmental "sensitive periods" have poor feeding skills, resulting in intractable food aversion (Illingworth and Lister 1964; Gisel et al. 1998; Kobayashi et al. 2003).

Recently, Ebihara et al. (2006) reported that olfactory stimulation using black pepper oil (BPO), a strong appetite stimulant, safely improves swallowing function in older people with swallowing dysfunction regardless of their level of consciousness. Olfaction is a primitive sense, and human infants have been shown to be responsive to olfactory stimuli (Schaal et al. 2004). This led us to speculate that intervention with BPO may facilitate oral intake in pediatric patients, which has not been addressed in previous studies.

The objective of this preliminary study was to assess whether BPO stimulation facilitates oral intake in pediatric patients receiving prolonged EN despite a continuous rehabilitation program for oral intake.

Patients and Methods

This study was performed from September 2006 to September 2007 at Takuto Rehabilitation Center for Children, Sendai, Japan. Before the intervention, physical condition and risks for aspiration were assessed. The assessment included observing the cough reflex and swallowing of saliva and a swallowing test with water and thickened 5%-glucose solution. A videofluoroscopic examination was performed in patients suspected of aspiration. Inclusion criteria for the trial comprised: (i) patients with chronic EN for more than 10 months despite a 6-month trial of a standard oral rehabilitation program; (ii) low risk of aspiration—specifically, only patients with a cough reflex and no dysphagia, or slight dysphagia for fluid only were included in the trial. Patients who had undergone tracheolaryngeal separation surgery were included because they had no risk of aspiration.

Ten patients {4 boys and 6 girls; aged 19-97 (51 ± 26 [mean ± S.D.]) months} with prolonged EN were included in this trial (Table 1). The duration of EN was 50 ± 27 months. In the swallowing test, taking water induced an occasional cough in Patients 4 and 7; in the videofluoroscopic examination, no intratracheal aspiration was observed in Patient 4, while Patient 7 aspirated a slight amount of water, but none of the thickened solution. Since Patients 1 and 8 had undergone tracheolaryngeal separation, no risk of aspiration existed despite disorganized swallowing. The parents or guardians of all patients gave their informed consent to participate in the study. The study protocol was approved by the ethics committee of Takuto Rehabilitation Center for Children, Sendai, Japan.

Olfactory stimulation using BPO was performed as reported previously with some modifications (Ebihara et al. 2006). Oral feeding was attempted after starving once or twice per day. Nasal stimulation with 100 μl of BPO (Yamamoto Perfumery, Osaka) was accomplished by administering BPO to the nostrils with a filter paper stick for 1 min just before the meal. In cases with tracheolaryngeal separation, BPO was directed to the nasal cavity by gentle fanning, in which case the BPO was also inevitably inhaled through the tracheostomy. Oral feeding was then attempted with pureed foods, and the amount of each meal was recorded. In bedridden patients, oral feeding was performed in the head-up tilt position. After the meal, liquid enteral nutrition was injected. In cases in which the amount of oral intake exceeded 100 g, the amount of oral intake was subtracted from the subsequent enteral nutrition. During oral feeding, a thin NG tube (6-8 French units) was left in place, considering the burden on pediatric patients and the risks of mal-location of the tube tip accompanied by frequent reinsertion of the tube. The effects of BPO were evaluated after 3 months of daily BPO trials. The statistical significance of changes in the amount of oral intake was determined using the Mann-Whitney's U-test.

TABLE 1. Clinical features of patients included in the BPO intervention trial.

Patient	Age/Sex	Diagnosis	Developmental delay (DQ)	Motor disabilities	Epilepsy (AED)	Neuro-imaging	Problems in swallowing	Dysphagia	Onset of EN	Type of EN	Operation
1	2y6m/M	Sequelae of HIE	Severe (DQ 22)	Bedridden	+ (PB)	Atrophy of basal ganglia	Poor swallowing movement	+	Birth	G	Gastrostomy, tracheolaryngeal separation
2	7y/M	PVL	Severe (DQ 34)	-	-	White matter atrophy	Food aversion	-	Birth	NG	Tracheostomy
3	2y5m/F	Costello syndrome	Severe (DQ 33)	Bedridden	-	Normal	Food aversion	-	Birth	NG	-
4	3y/M	Sequelae of HIE	Severe (DQ 26)	Bedridden	+ (CZP)	Cortical atrophy	Occasional choking, delayed oral stage	-	2y1m	NG	-
5	5y3m/F	Sequelae of HIE	Severe (DQ 6)	Bedridden	+ (VPA, DZP)	White matter atrophy	No concern about food, delayed oral stage	-	Birth	G	Gastrostomy
6	3y10m/M	Russell-Silver syndrome	Normal (DQ 91)	-	-	Normal	No concern about food, delayed oral stage	-	Birth	G	Gastrostomy, Nissen fundoplication
7	8y1m/F	Miller-Dieker syndrome	Severe	Bedridden	+ (VPA)	Lissencephaly	Slight aspiration of fluid	+	Birth	G	Gastrostomy
8	1y7m/F	PVL	Severe	Bedridden	+ (VPA, CZP, ZNS)	White matter atrophy	Poor swallowing movement	+	Birth	G	Gastrostomy, tracheolaryngeal separation
9	5y6m/F	PVL	Borderline (DQ 79)	-	-	White matter atrophy	No concern about food, delayed oral stage	-	Birth	IOE	-
10	3y4m/F	CP, MR (unknown etiology)	Severe	Bedridden	+ (ZNS, VPA)	Cortical atrophy	No concern about food, delayed oral stage	-	Birth	NG	-

BPO, black pepper oil; y, year(s); m, month(s); F, female; M, male; HIE, hypoxic ischemic encephalopathy; PVL, periventricular leukomalacia; CP, cerebral palsy; MR, mental retardation; DQ, developmental quotient; AED, antiepileptic drug; PB, phenobarbital; CZP, clonazepam; DZP, diazepam; VPA, valproate; ZNS, zonisamide; G, gastrostomy; NG, nasogastric tube; IOE, intermittent oroesophageal tube.

Results

Table 2 shows the results of the BPO intervention. Eight of the ten patients successfully completed 3 months of the intervention. The intervention was discontinued before 3 months in two patients because the patients' family found the odor of BPO unbearable (Patient 9) or frequent coughing occurred on smelling the BPO (Patient 10), although BPO did not elicit any other serious complications in any patient tested. The coughing during BPO stimulation in Patient 10 was caused not by increased salivation, but by stimulation of the airway by BPO. The body weights of the eight patients showed normal growth, with values before and after the BPO intervention of 12.3 ± 3.7 and 12.6 ± 4.0 (mean ± S.D.) kg, respectively.

Of the eight patients who completed 3 months of the BPO intervention, five responded to the intervention and showed a distinct increase in oral intake (Patients 1 through 5), although complete cessation of EN was not achieved. As shown in Table 2, the increase was accompanied by desirable effects, such as facilitated appetite, reduced drooling, and distinct swallowing movements. In Patient 5, the amount of oral intake was temporarily reduced when the number of seizures increased during the intervention, although the amount of intake was eventually increased. In Patient 6, the average amount of oral intake was increased slightly but was not stable among meals. Patients 7 and 8 did not respond to BPO. Patient 7 had Miller-Dieker syndrome with profound cerebral malformation and Patient 8 had severe white matter volume loss. As summarized in Fig. 1, BPO intervention significantly increased the amount of oral intake ($p = 0.016$). As described above, the intervention was discontinued before 3 months in Patients 9 and 10, and their data are not plotted in Fig. 1.

Discussion

This study investigated the effects of BPO stimulation in pediatric patients receiving long-term EN who did not respond to a conventional oral feeding rehabilitation program. Although complete discontinuation of EN was not achieved, the 3-month BPO intervention facilitated oral intake in these patients.

Swallowing is an elaborate mechanism that enables the ingestion of fluids and solid foodstuffs without aspiration. This mechanism is regulated by a widespread neuronal network spread over the cerebrum, cerebellum, and brain stem (Humbert and Robbins 2007). Therefore, various diseases

Table 2. Summary of the results of BPO intervention.

Patient	Result	Observation after 3 months of the BPO trial	Adverse effects
1	Effective	Increased oral intake, reduced drooling, obvious swallowing movements	None
2	Effective	Increased oral intake, shows an interest in food (sniffing, eating by himself)	None
3	Effective	Increased oral intake, facilitated oral stage	None
4	Effective	Increased oral intake, choking during meals disappeared, facilitated oral stage	None
5	Effective	Increased oral intake, facilitated oral stage	None
6	Equivocal	Increased oral intake, but not stable	None
7	Not obvious	No obvious changes	None
8	Not obvious	No obvious changes	None
9	Discontinued	No obvious changes	Family could not tolerate the odor of BPO
10	Discontinued	No obvious changes	Frequent coughing during BPO stimulation

affecting the central nervous system are frequently accompanied by swallowing dysfunction. Among the brain areas, the insular cortex has been shown to play a major role in the mechanism of the effects of BPO. The smell of BPO potently stimulates the insular cortex and orbitofrontal cortex (Ebihara et al. 2006). Functional imaging studies have revealed that the insular cortex plays significant roles in both the sensation of appetite and in the generation of voluntary swallowing (Tataranni et al. 1999; Humbert and Robbins 2007). Therefore, BPO may exert beneficial effects on both appetite and swallowing *via* activation of the insular cortex. In addition, piperine, a major source of BPO flavor, is an agonist of the transient receptor potential vanilloid 1 receptor (TRPV1) causing systemic release of substance *P* (SP) (Szallasi 2005; Ebihara et al. 2006). SP has been shown to facilitate the swallowing process. Indeed, serum SP levels are increased by the smell of BPO (Yamaya et al. 2001). Stimulation with BPO may also improve swallowing function through the action of SP.

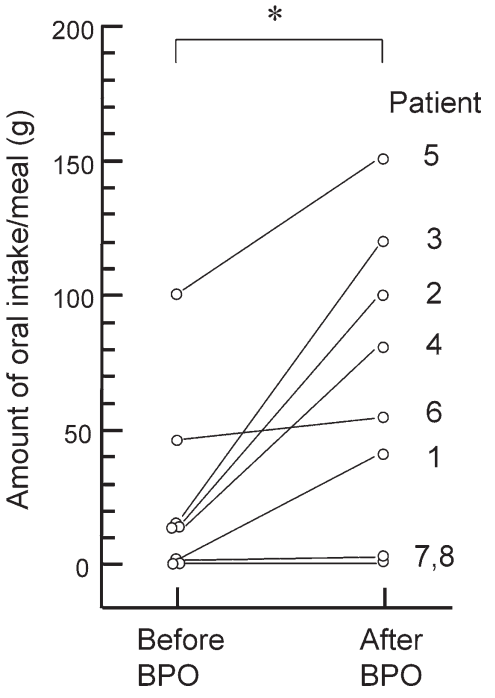

Fig. 1. Changes in the amount of food ingested orally.
Plots represent the average amount of oral intake during 1 week of observation before and after 3 months of BPO therapy. Lines connect the plots from the same patient. Numbers beside the plots indicate the patient numbers, corresponding to those in Table 1. Asterisks indicate statistical significance (Mann-Whitney's U-test, $p < 0.05$). Data from Patients 9 and 10 are not included in the figure and statistics because their therapies were discontinued prior to 3 months (see text).

In this study, BPO intervention had beneficial effects on oral intake in patients affected in various regions of the brain, including the cortex, white matter, and basal ganglia. Magnetic resonance imaging (MRI) showed that the patients in whom BPO was effective had preserved cerebral tissue volume irrespective of the severity of their developmental disabilities. However, Patient 8 in whom BPO was not effective showed severe and diffuse white matter loss. Patient 7, who had Miller-Dieker syndrome, also did not respond to BPO. In Miller-Dieker syndrome, cerebral tissue volume is maintained but the tissue is severely malformed (lissencephaly) due to an abnormal Lis1 gene (Dobyns et al. 1993). Impairment of the Lis1 gene causes disorganization of the olfactory bulb (Hirotsune et al. 1998), resulting in inefficient olfaction, which would render BPO stimulation ineffective. Overall, BPO intervention seemed to be generally effective, although patients with severe cerebral tissue loss or profound malformation may not show a response to this appetite stimulant. Control of seizures also seemed to be important for the efficacy of BPO.

The effect of BPO seemed to be correlated with appetite in this study, and caused an increase in the oral intake. In addition, an improvement in swallowing movements was observed during the BPO intervention, as shown in Table 2. In elderly patients with dysphagia, BPO stimulation shortened the latency of the swallowing reflex and reduced pooling in the recessus piriformis, both of which imply ameliorated swallowing dysfunction (Ebihara et al. 2006). Although complete functional measurements of swallowing were not performed to reduce the burden on the patients, BPO may remediate swallowing dysfunction in pediatric cases. Although olfactory stimulation with BPO should be applied carefully in patients

with dysphagia, further investigation of the effects of BPO on dysphagia are warranted based on our results.

In conclusion, olfactory stimulation with BPO is a potentially effective means to facilitate oral intake in pediatric patients with prolonged EN. Although the effect of BPO was limited, it was still beneficial, especially in patients who did not respond to conventional rehabilitation intervention. BPO stimulation may be useful for facilitating oral intake when used in combination with conventional methods. Further investigations are required to determine the efficacy, application, and limitations of the BPO intervention.

References

Dobyns, W.B., Reiner, O., Carrozzo, R. & Ledbetter, D.H. (1993) Lissencephaly. A human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13. *JAMA*, **270**, 2838-2842.

Ebihara, T., Ebihara, S., Maruyama, M., Kobayashi, M., Itou, A., Arai, H. & Sasaki, H. (2006) A randomized trial of olfactory stimulation using black pepper oil in older people with swallowing dysfunction. *J. Am. Geriatr. Soc.*, **54**, 1401-1406.

Gisel, E.G., Birnbaum, R. & Schwartz, S. (1998) Feeding impairments in children: diagnosis and effective intervention. *Int. J. Orofac. Myol.*, **24**, 27-33.

Hirotsune, S., Fleck, M.W., Gambello, M.J., Bix, G.J., Chen, A., Clark, G.D., Ledbetter, D.H., McBain, C.J. & Wynshaw-Boris, A. (1998) Graded reduction of Pafah1b1 (Lis1) activity results in neuronal migration defects and early embryonic lethality. *Nat. Genet.*, **19**, 333-339.

Humbert, I.A. & Robbins, J. (2007) Normal swallowing and functional magnetic resonance imaging: a systematic review. *Dysphagia*, **22**, 266-275.

Illingworth, R.S. & Lister, J. (1964) The critical or sensitive period, with special reference to certain feeding problems in infants and children. *J. Pediatr.*, **65**, 839-848.

Kobayashi, Y., Tanaka, S. & Onuma, A. (2003) "Bottle feeding dependency" in children with developmental retardation. *No To Hattatsu*, **35**, 153-158. (in Japanese)

Kumode, M. (2003) Management of nutrition in children and adults with severe motor and intellectual disabilities. *No To Hattatsu*, **35**, 206-210. (in Japanese)

Munakata, M., Onuma, A., Kobayashi, Y., Haginoya, K., Yokoyama, H., Fujiwara, I., Yasuda, H., Tsutsui, T. & Iinuma, K. (2006) A preliminary analysis of trace elements in the scalp hair of patients with severe motor disabilities receiving enteral nutrition. *Brain Dev.*, **28**, 521-525.

Ohrui, T. (2005) Preventive strategies for aspiration pneumonia in elderly disabled persons. *Tohoku. J. Exp. Med.*, **207**, 3-12.

Schaal, B., Hummel, T. & Soussignan, R. (2004) Olfaction in the fetal and premature infant: functional status and clinical implications. *Clin. Perinatol.*, **31**, 261-285.

Sleigh, G., Sullivan, P.B. & Thomas, A.G. (2004) Gastrostomy feeding versus oral feeding alone for children with cerebral palsy. *Cochrane Database Syst. Rev.*, **2**, CD003943.

Szallasi, A. (2005) Piperine: researchers discover new flavor in an ancient spice. *Trends Pharmacol. Sci.*, **26**, 437-439.

Tataranni, P.A., Gautier, J.F., Chen, K., Uecker, A., Bandy, D., Salbe, A.D., Pratley, R.E., Lawson, M., Reiman, E.M. & Ravussin, E. (1999) Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. *Proc. Natl. Acad. Sci. USA*, **96**, 4569-4574.

Yamaya, M., Yanai, M., Ohrui, T., Arai, H. & Sasaki, H. (2001) Interventions to prevent pneumonia among older adults. *J. Am. Geriatr. Soc.*, **49**, 85-90.