Effectiveness of low-dose intravenous fentanyl for postoperative headache management after neck clipping of ruptured intracranial aneurysms

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Abbreviations: SAH subarachnoid hemorrhage, NSAIDs nonsteroidal antiinflammatory drugs, WFNS World Federation Neurological Surgeons, CSF cerebrospinal fluid, MCA middle cerebral artery, NRS numeric rating scale, mRS modified Rrankin score, NMDA N-methyl-D-aspartic acid, PCH postcraniotomy headache

Abstract

Background: After subarachnoid hemorrhage, headache management is often difficult owing to the need to use multiple analgesic drugs. Fentanyl is an opioid we can use after surgery, and it can decrease pain after subarachnoid hemorrhage. The aim of this study was to investigate the effectiveness and safety of fentanyl for management of headache after subarachnoid hemorrhage.

Methods: Twenty-two patients who underwent surgical clipping for ruptured intracranial aneurysms and complained of severe headache after the surgery were enrolled. Among them, 9 patients were given fentanyl combined with other analgesic drugs. The numeric rating scale score and dietary intake were measured in the acute phase after the subarachnoid hemorrhage.

Results: The numeric rating scale scores were significantly lower in the fentanyl (+) group. The maximum numeric rating scale decreased to less than 5 points within 16.5 ± 2.9 days in the fentanyl (-) group and within 12.0 ± 2.6 days in the fentanyl (+) group. The median numeric rating scale decreased to less than 5 points over 14.0 ± 4.2 days in the fentanyl (-) group and over 7.7 ± 3.8 days in the fentanyl (+) group. At day 14, the fentanyl (+) group showed significantly better dietary intake than that of the fentanyl (-) group.

Conclusions: Using fentanyl after surgical clipping for ruptured intracranial aneurysms might decrease

headache and produce few adverse effects. Adequate headache control showed improved dietary intake after subarachnoid hemorrhage.

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) occurs at an annual rate of about 20 individuals per 100 000 people in Japan[1,2]. Headache after SAH is sometimes very severe and is described as the worst headache of one's life. It persists for a prolonged time and often requires treatment with several analgesic drugs. Moreover, the continued headache curtails the patient's ability to perform activities of daily living. For severe headache, the 2013 European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage recommend acetaminophen and opioids[3]. However, evidence for the use of opioids is insufficient and supported by expert opinion only. Furthermore, the American Heart Association Stroke Guidelines and the Japan Guidelines for the Management of Stroke also do not offer evidence-based recommendations for using opioids to manage headache after SAH[4,5]. Among those analgesics supported by clinical evidence, the first choice for headache after SAH is acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs), but the effect is limited in many cases. Opioids are an optional treatment; however, they can induce sedation and respiratory depression as adverse effects. In the management of the acute phase of SAH, these conditions may mask neurologic events due to rebleeding or ischemic events from vasospasm. Fentanyl is a potent synthetic μ-receptor-stimulating opioid that is approved

for postoperative pain and can be administered intravenously[6]. Low-dose intravenous fentanyl can be used for postclipping pain and potentially has fewer adverse effects, but its efficacy for headache after SAH is unknown. The aim of this study was to investigate the effectiveness and safety of fentanyl for management of headache after SAH.

Methods

Patients

We conducted a retrospective study of SAH patients treated at Tsukuba Medical Center Hospital. Forty-two patients (13 men, 29 women; average age, 59.6 ± 13.5 years) who underwent clipping for a ruptured intracranial aneurysm between January 2013 and April 2017 were included. Their conditions were classified as World Federation Neurological Surgeons (WFNS) grade I, II, or III on admission and required intubation within 48 hours after surgery. Patients with WFNS grade IV or V were excluded because the severity of the headache could not be assessed.

SAH management

At the emergency department, the patients were treated with antihypertensive (nicardipine), analgesic (pentazocine), and sedative (dexmedetomidine) drugs. Computed tomography angiography

or digital subtraction angiography was performed to find the aneurysm or another cause of the SAH. The aneurysms were immediately treated, mainly with endovascular coiling. In almost all the coiling cases, spinal drainage systems were placed to remove SAH-related blood from the cerebrospinal fluid (CSF) and to control the intracranial pressure. Clipping was selected in cases in which endovascular coiling was technically difficult, ie, aneurysms in the middle cerebral artery (MCA) or distal part of the anterior cerebral artery or space-occupying hematomas due to an anterior circulation aneurysm, anterior communicating artery, or internal carotid artery aneurysm endovascular coiling of which was technically difficult. Cisternal, ventricular, or spinal drainages were placed case by case after the clipping. After the aneurysm treatment, intravenous fasudil hydrochloride and ozagrel sodium were used. An oral statin and eicosapentaenoic acid ethyl ester, and cilostazol were also given for preventing vasospasm.

Headache management

For the headache, NSAIDs, acetaminophen, or a tramadol-acetaminophen combination was used alone or in combinations. Postoperative headache was estimated by use of a numeric rating scale (NRS) in which 0 represents no pain and 10 represents the worst pain ever experienced. Such NRSs are applicable for unidimensional assessment of pain intensity in most settings[7]. In our study, the

patients were asked to evaluate their pain according to the NRS several times (usually 3 or 4 times) a day. Headache severity was estimated according to the daily maximum and mean NRS. Severe headache was defined according to a maximum NRS of over 8 points within 2 days with more than 2 analgesic drugs taken. From August 2015, low-dose intravenous fentanyl at a dose of 1 to 2 μg/kg/day was added to these drugs depending on the pain level for patients with severe headache. Bolus administration of fentanyl was not performed to avoid adverse events.

Data collection

Data were collected on patient age; sex; aneurysm location; WFNS score before treatment; Fisher group at the first head CT (group 1, with no blood detected; group 2, with a diffuse deposition or a thin layer with all vertical layers of blood less than 1 mm thick; group 3, with localized clots and/or vertical layer of blood of 1 mm or greater in thickness; group 4, with diffuse or no subarachnoid blood, but with intracerebral or intraventricular clots); symptomatic vasospasm (with neurologic deficit); hydrocephalus requiring shunt surgery; dietary intake; days in the hospital; and modified Rankin Score (mRS) at discharge. Dietary intake, between 0% and 100%, was estimated according to the visual judgment of the nurse in charge.

Statistical analysis

Each value was expressed as the mean ± standard deviation. For comparison between 2 groups, the chi-square, Fisher exact, and Mann-Whitney U tests were used. The threshold for significance was $P < 0.05$.

Results

Forty-two patients underwent aneurysm clipping. In 22 of the patients (52.4%), the headache was severe. Of the 22 patients with severe headache, 9 patients (40.9%) received fentanyl (fentanyl (+) group), and 13 patients (59.1%) did not (fentanyl (-) group). Table 1 shows the patients' background characteristics. The severity of headache and use of fentanyl were associated with the background. Fentanyl was started from 4.4 ± 2.5 days after clipping and used for a mean of 5.1 days. The average daily dose of fentanyl was 1.38 ± 0.4 μg/kg/day. Adverse effects occurred in 1 case—a patient who complained of nausea 3 days after beginning fentanyl—and the fentanyl administration was stopped. Decrease of consciousness level or respiratory depression was not detected in any of the cases. Both the median and the maximum NRS decreased in the fentanyl group (Figure 1A,B). The maximum NRS decreased to less than 5 points within 16.5 ± 2.9 days in the fentanyl (-) group and within 12.0 ± 2.6 days in the fentanyl (+) group. The median NRS decreased to less than 5 points within 14.0 ± 4.2 days

in the fentanyl (-) group and within 7.7 ± 3.8 days in the fentanyl (+) group. In both groups, the NRS did not increase by more than 5 points again. Both scores significantly decreased with the fentanyl use (Table 2). Dietary intake increased in the fentanyl (+) group from day 9. At day 14, the fentanyl (+) group showed significantly better dietary intake than that of the fentanyl (-) group (Figure 2). Use of fentanyl was not associated with symptomatic vasospasm, days in the hospital, or mRS at discharge.

Representative case (Figure 3)

A 58-year-old man had severe headache and nausea. Head CT and CT angiography showed SAH mainly in the right sylvian fissure and a right MCA aneurysm, about 8 mm in size (Figure 3 A,B). On the same day, aneurysm clipping was performed. After the operation, the severe headache persisted for 2 days despite treatment with oral acetaminophen and NSAIDs. Intravenous fentanyl was started from day 3. After that, the median NRS decreased and the dietary intake increased gradually. Even after tapering of fentanyl, the headache was controlled with oral analgesic drugs only (Figure 3C).

Discussion

Headache occurs in more than 90% of patients after SAH[8,9]. Such a headache is severe and persists[10,11] for several reasons. First, inflammatory or hemolysis products cause continuous

meningeal irritation[12-15]. Next, activation of N-methyl-D-aspartic acid (NMDA) receptors facilitates pain transmission in the central nervous system, which leads to hyperalgesia after SAH[16]. Surgical clipping adds postcraniotomy headache (PCH). PCH occurs for several reasons, including muscle injury, adherence of the muscle to the dura mater, peripheral nerve injury, and central sensitization[17]. A previous report showed that compared with coil embolization, clipping increased the risk of headache development after treatment of a ruptured intracranial aneurysm because of the craniotomy[8]. These mixed causes augmented the headache after SAH.

Several reports showed the factors associated with headache severity after SAH. Age, sex, Fisher grade, onset time, and aneurysm location were not associated with headache severity[9]. Another report showed that patients with Hunt and Hess grade II SAH had severe headache, and a Hijdra score (measurement of blood volume in the subarachnoid space; range 0–30, 30 being the maximum volume) of 0 to 10 was associated with less headache[10]. That report showed that Hunt and Hess grade I was associated with mild headache, and that Hunt and Hess grade III was associated with drowsiness or confusion, resulting in less pain being felt, which explained why Hunt and Hess grade II patients felt severe pain. In contrast to these previous reports, we found no such relationships with headache severity after SAH.

The main medications for management of headache are NSAIDs and acetaminophen. NSAIDs might be neuroprotective and have antiinflammatory effects. Systemic levels of interleukin-6 and C-reactive protein were decreased in SAH patients treated with NSAIDs and acetaminophen[18]. Direct intracranial delivery of ibuprofen in a rabbit model of SAH decreased the incidence of vasospasm[19]. However, ketoprofen administration impaired platelet aggregation and increased the risk of hemorrhage after surgical clipping for ruptured aneurysm[20]. The MASH study reported that aspirin after aneurysm treatment did not reduce the occurrence of delayed ischemic neurologic deficit after SAH[21]. For these reasons, NSAIDs and acetaminophen are considered to be effective for SAH patients in some respects. In addition, headache management after SAH was not adequate even with multiple analgesics including NSAIDs and acetaminophen[10]. In this study, the maximum NRS remained higher than 6 and the median NRS, higher than 5 until day 14 after SAH. Some reports have been published on other medications for management of headache after SAH. Magnesium is a calcium channel and an NMDA receptor antagonist, and a report showed that magnesium intake in migraine patients reduced the number of days with headache[22]. Moreover, elevated serum magnesium levels were associated with less headache after SAH[16]. However, the Magnesium for Aneurysmal Subarachnoid Hemorrhage (MASH-2) trial showed that magnesium is not superior to placebo for reduction of poor

outcomes after SAH[23]. Pregabalin and gabapentin are analogs of γ-aminobutyric acid and have shown efficacy in conditions in which features of central sensitization are present[24]. A report showed preoperative use of pregabalin reduced postoperative pain scores[25]. Another report showed gabapentin were potentially effective as a narcotic-sparing agent in headache after SAH[26]. However, high-dose usages of gabapentin carry the possibility of addiction and dependence[27].

Opioids are another option in the management of postcraniotomy or SAH patients. In particular, intravenous fentanyl can be used after surgery. Fentanyl is a completely synthetic μ-receptor-stimulating opioid. Analgesia may occur within 1 to 2 minutes of intravenous administration[6]. Opioids usually produce such effects as sedation, nausea, and respiratory depression, but fentanyl does so less frequently than other opioids because it does not increase plasma histamine. In general, postoperative intravenous fentanyl is used at a dose of 1 to 2 μg/kg/day. If the patient's weight is 50 kg, fentanyl is used at a dose of 1.2 to 2.4 mg (60–120 mg; morphine equivalent) per day. However, in clinical practice, neurosurgery patients receive small doses of fentanyl because of the fear of adverse effects. The efficacy of fentanyl was not proven in patients with headache after SAH who were given a total opioid dose of 18 mg per day in morphine equivalents[10]. In another study, acetaminophen plus fentanyl usage did not improve the headache after SAH [11]. In that study, a mean

daily opioid dose of 16.5 mg in morphine equivalents was also used. In our study, fentanyl was used at a dose of 1.2 to 2.4 mg per day, with few adverse effects. Our results showed that such doses of fentanyl were safe and effective in patients with headache after SAH.

In this study, we demonstrated an increase in dietary intake in the fentanyl group. We supposed that good pain control would provide a positive effect on dietary intake without the adverse effects associated with fentanyl. However, the amount of the intake was estimated according to visual judgment and with a little variability between the evaluators.

Our study has some limitations. First, sensitivity to fentanyl varies among individuals. The single nucleotide polymorphism of the human *OPRM1* gene encoding the μ-opioid receptor influences the analgesic effects of opioids[28]. In particular, the A118G variant receptor binds with β-endorphin, an endogenous opioid that activates the μ-opioid receptor, approximately 3 times more tightly than the most common allelic form of the receptor[29]. The A118G variant is present in about 44% of Japanese people, compared with in 10% of Western people[28,30]. Therefore, the amount of fentanyl needed may differ for Japanese. Second, this study was a nonrandomized retrospective study with a small sample size, and fentanyl was used in only 9 cases. Furthermore, more of the male patients that the female patients were treated with fentanyl, and even fewer of those treated with fentanyl had anterior

communicating artery aneurysms, rendering the overall comparison statistically insignificant. We must increase the number of cases to examine the effect of these factors. For these reasons, it might be difficult to draw a strong conclusion on the basis of our results. Further randomized controlled trials involving a larger number of patients are required. Third, the pretreatment NRS was not evaluated and coil embolization cases were excluded from this study. If we compare the NRS of the pretreatment and posttreatment phases or of the neck clipping and coil embolization cases, we could estimate the impact of the surgery and PCH and the effectiveness of fentanyl for headache after subarachnoid hemorrhage.

Conclusion

In summary, using fentanyl after surgical clipping of ruptured cerebral aneurysms might decrease headache and have few adverse effects. Adequate headache control may improve dietary intake after SAH.

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Statement of ethics

This study was approved by the institutional review board of the Tsukuba Medical Center Hospital (2018-074) and conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. After information disclosure, all the patients or their family members as legal representatives provided informed consent and permission for publication.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Baseline characteristics of the patients

Table 2. Days until NRS score decreased to less than 5 points. Both the median and the maximum

NRS scores decreased rapidly and significantly in the fentanyl group

Figure 1. NRS score comparison. Median (A) and maximum (B) NRS. The median and maximum NRS were both lower in the fentanyl (+) group.

Figure 2. Comparison of dietary intakes after subarachnoid hemorrhage. The fentanyl (+) group showed better intake on day 14.

Figure 3. Illustrative case. Head CT showed subarachnoid hemorrhage mainly in the area of the right sylvian fissure (A). CT angiography showed a right MCA aneurysm about 8 mm in size with a bleb on top of the dome (B). The right bar shows the NRS, and the left bar, the amount of dietary intake (%). Fentanyl was used together with oral analgesic drugs, and the amount was adjusted according to the headache severity (C).

Table1

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	total (n=42)			Severe headache group (n=22)		
	Severe headache(-) (n=20)	Severe headache(+) (n=22)	P value	Fentanyl (-) (n=13)	Fentanyl (+) (n=9)	P value
Age	60.4±12.5	58±14.9	0.88	56.3±16.0	62.7±13.2	0.49
Sex(male : female)	7:13	6:14	0.73	2:11	4:05	0.13
WFNS score			0.54			0.8
I	13	14		8	6	
II	6	8		5	3	
III	1	0		0	0	
Fisher group			0.72			0.93
2	12	12		7	5	
3	8	10		6	4	
Aneurysm location			0.45			0.39
Acom	5	8		6	2	
IC-PC	8	4		1	3	
MCA	6	8		4	4	
IC-Acho	1	1		1	0	
distal ACA	0	1		1	0	
Cisternal/ventricular/lumber drain	17	20	0.74	12	8	0.9
Symptomatic spasm	3	2	0.61	1	1	0.81
Hydrocephalus	3	3	0.91	2	1	0.81
In hospital days	33.3±18.7	32.7±16.2	0.62	34.1±16.8	30.8±16.1	0.26
mRS at discharge			0.24			0.39
0-2	17	21		12	9	
3-5	3	1		1	0	
6	0	0		0	0	

Table2

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	Fentanyl (-)	Fentanyl (+)	P value
NRS (maximum)	16.5±2.9	12.0±2.6	0.003
NRS (median)	14.0±4.2	7.7±3.8	0.006

Figure1

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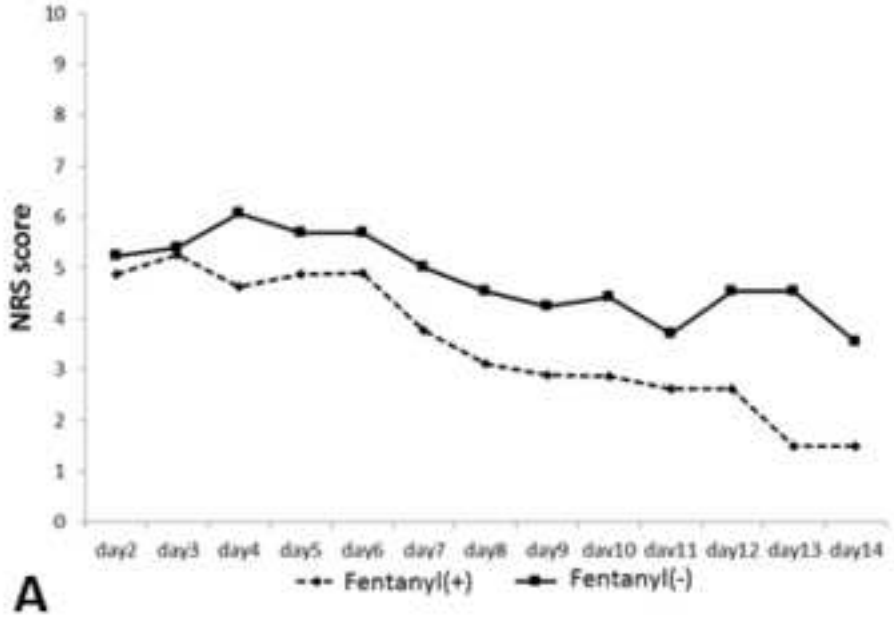

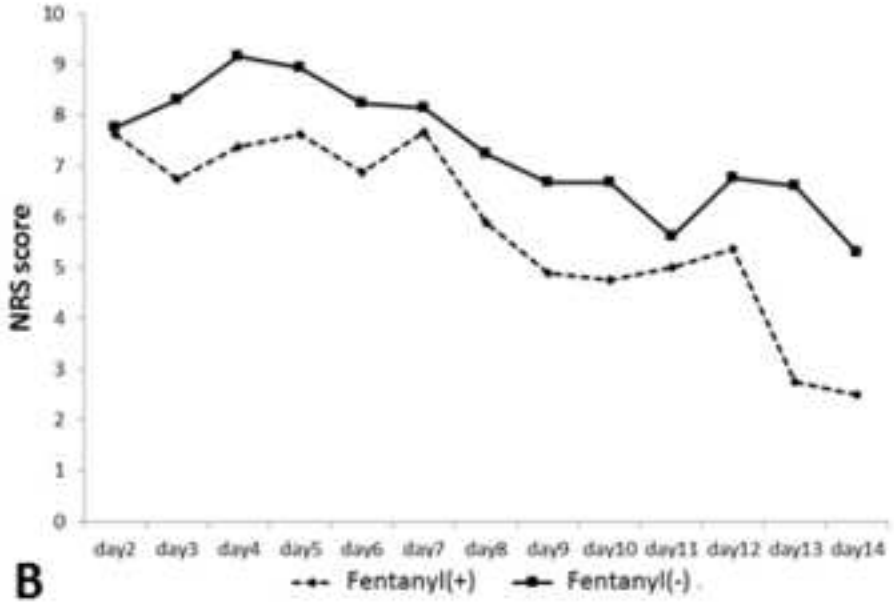

Figure2

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Figure3

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