ORIGINAL RESEARCH

Twelve-year single critical care center experience of nicardipine prolonged-release implants in patients with subarachnoid hemorrhage: a propensity score matching analysis

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ABSTRACT

Objective To develop a nicardipine prolonged-release implant (NPRI) to prevent cerebral vasospasm in patients with subarachnoid hemorrhage in 1999, which may be used during craniotomy, and report the results of our recent 12-year single critical care center experience.

Methods Of 432 patients with aneurysmal subarachnoid hemorrhage treated between 2007 and 2019, 291 were enrolled. 97 Patients were aged >70 years (33%), 194 were female (67%), 138 were World Federation of Neurological Societies grades 1, 2, and 3 (47%), 218 were Fisher group 3 (75%), and 243 had an anterior circulation aneurysm (84%). Using a propensity score matching method for these five factors, the severity of cerebral vasospasm, occurrence of delayed cerebral infarction, and modified Rankin Scale (mRS) score at discharge were analyzed.

Results One hundred patients each with or without NPRI were selected, and the ratios of coil/clip were 0/100 and 88/12, respectively. Cerebral vasospasm and delayed cerebral infarction were both significantly less common in the NPRI group (p=0.004, OR=0.412 (95% CI 0.223 to 0.760) and p=0.005, OR=0.272 (95% CI 0.103 to 0.714, respectively); a significant difference was seen in the mRS score at discharge by Fisher's exact test (p=0.0025). A mRS score of 6 (dead) was less common in the group with NPRI, and mRS scores of 0 and 1 were also less common. No side effects were seen.

Conclusions NPRIs significantly reduced the occurrence of cerebral vasospasm and delayed cerebral infraction without any side effects. The NPRI and non-NPRI groups showed different patterns of short-term outcomes in the single critical care center, which might have been due to selection bias and patient characteristics. Differences in outcomes may become clear in comparisons with patients treated by craniotomy.

INTRODUCTION

Delayed cerebral ischemia (DCI) resulting from cerebral vasospasm is an important cause of severe complications following aneurysmal subarachnoid hemorrhage (SAH). Although the prevention of DCI due to the development of cerebral vasospasm has been extensively examined, only nimodipine or other calcium antagonists administered orally or intravenously are recommended for reducing the risk of a poor outcome related to cerebral vasospasm in the American Heart Association Stroke Council guidelines for the management of aneurysmal SAH.[1] However, oral nimodipine therapy did not affect vessel calibers based on angiography. Additional and alternative preventive treatments for vasospasm are needed, particularly those specifically targeting the dilatation of cerebral vessels.

We developed an implant for local treatment that may be implanted intracranially at the time of surgery for aneurysm clipping. We previously published several studies on the efficacy and safety of nicardipine prolonged-release implants (NPRIs) to prevent vasospasm in patients with SAH.[2–5] Vasospasm was completely prevented in the arteries of cisterns with thick clots, in which vasospasm was strongly expected, by placing NPRIs adjacent to arteries during surgery, without side effects.

We have been using NPRIs that are produced in our hospital pharmacy. Based on the Pharmaceutical Affairs Law in Japan, we may only use drugs in the hospital in which they are produced and cannot supply them to other hospitals in Japan. A clinical trial using commercially available NPRIs is planned in Europe.[6] We herein report the results of a 12-year single critical care center experience.

MATERIALS AND METHODS

This retrospective study used the prospectively accumulated database of 432 patients with aneurysmal SAH in Tokyo Women's Medical University Medical Center East who underwent treatment for ruptured aneurysms during a 12-year period between April 2007 and March 2019.[7] The study was approved by the institutional review board of Tokyo Women's Medical University (No 1812). We excluded patients operated on 4 days or later after onset, those who underwent surgery for proximal occlusion or trapping with or without bypass, or those who died within 14 days.

One hundred and forty-one patients (32.6%) were excluded and, thus, 291 patients met the above criteria (table 1).

The characteristics of these patients are shown in table 1. No side effects were seen. The numbers of

Table 1 Characteristics of 291 patients with subarachnoid hemorrhage

Characteristics	N (%)
Age (years)	26~92 (average, 63.3)
Age >70 years	97 (33)
Female	194 (67)
WFNS grades 1, 2, and 3	138 (47)
Fisher group 3	218 (75)
Anterior circulation aneurysm	243 (84)
Coil/clip	146/145
NPRIs used	130 (45)
Cerebral vasospasm	100 (34)
Delayed cerebral infarction	36 (12)
Rescue therapy (intra-arterial fasudil administration)	26 (9)
mRS score 0, 1, or 2 at discharge	103 (35)
Total	291

mRS, modified Rankin Scale; NPRI, nicardipine prolonged-release implant; WENS, World Federation of Neurological Societies.

patients with more advanced World Federation of Neurological Societies (WFNS) grades and Fisher group 3 were higher than in other studies because most of our patients came through a critical care and emergency center. Since there was a bias and discrepancy in the number of patients with or without NPRIs, a case-matched study was conducted by one of the authors (YS), who did not participate in other aspects of the present study and was blinded to the final outcomes. Patient selection was performed by the propensity score matching method with a Greedy 5-To-1 Digit-Matching algorithm for five clinical factors (age, sex, WFNS grade, Fisher group, and aneurysm location). After all propensity score matches had been performed, we compared baseline covariates between the two groups. Ultimately, 100 patients were selected in each group (table 2). P values after matching were >0.05 for all clinical factors, except for the aneurysm treatment (coil embolization or clipping).

A rod-shaped pellet (2 mm in diameter, 10 mm in length, containing 4 mg of nicardipine) was prepared by heat compression, described in detail elsewhere.[2–5] These pellets were placed in the cistern of the internal carotid artery (ICA), middle cerebral artery (MCA), and/or the anterior cerebral artery, in which thick clots existed, and, thus, vasospasm related to DCI was highly probable. The number of pellets and location of the placement depended on the amount and site of the subarachnoid clot in the preoperative CT or from the operative field and in craniotomy.

Table 2 Characteristics of 200 patients with subarachnoid hemorrhage selected by the propensity score matching method

	NPRIs	No NPRIs	P value
Age (years)	63.5	64.3	0.6654
Age >70 years	67	61	0.3768
Female	65	70	0.4503
WFNS grades 1, 2, and 3	40	45	0.4745
Fisher group 3	75	72	0.6308
Anterior circulation aneurysm	96	96	1.0000
Coil/clip	0/100	88/12	<0.0001

NPRI, nicardipine prolonged-release implant; WFNS, World Federation of Neurological Societies.

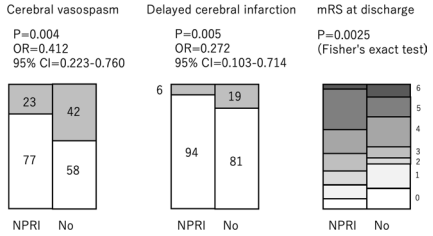

Figure 1 Results of nicardipine prolonged-release implants (NPRIs) analyzed by propensity score matching. mRS, modified Rankin Scale.

Cerebral vasospasm was assessed by angiography/3D CT angiography on days 7–12 in all patients; cerebral vasospasm was judged to be positive when the vessel diameter was <50% of the baseline. Delayed cerebral ischemia was assessed by the delayed occurrence of cerebral infarction other than primary brain damage, a low-density area associated with hematoma, and/or by the surgical procedure. Outcomes were assessed by the modified Rankin scale (mRS) score at discharge.

RESULTS

One hundred patients each with/without NPRIs were selected by propensity score matching (table 2) and the ratios of coil/clip were 0/100 and 88/12, respectively. Cerebral vasospasm and delayed cerebral infarction were both significantly less common in the NPRI group (p=0.004, OR=0.412 (95% CI 0.223 to 0.760) and p=0.005, OR=0.272 (95% CI 0.103 to 0.714), respectively); there was a significant difference in mRS score at discharge by Fisher's exact test (p=0.0025)figure 1. A mRS score of 6 (dead) was less common in the NPRI group, while mRS scores of 0 and 1 were also less common.

figure 1

The efficacy and limitations of this local treatment are shown with an illustrative patient in figure 2. The patient was diagnosed with SAH with a left sylvian hematoma ruptured from a left ICA aneurysm. Six NPRIs were placed along the left MCA during surgery. The patient developed severe vasospasm and

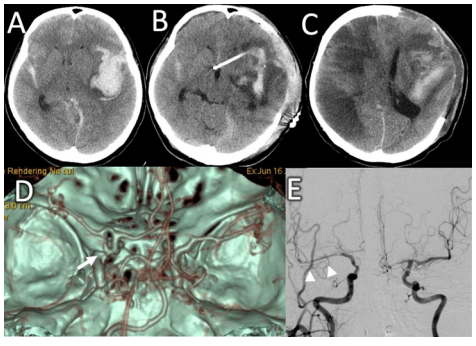

Figure 2 A patient was diagnosed with subarachnoid hemorrhage with a left sylvian hematoma ruptured from a left internal carotid artery (ICA) aneurysm. Six NPRIs (nicardipine prolonged-release pellets) were placed along the left middle cerebral artery (MCA) during surgery. The patient developed severe vasospasm and large cerebral infarction on the contralateral side, whereas the ipsilateral MCA with NPRIs did not. (A) CT on admission showed a large sylvian hematoma on the left side. (B) Postoperative CT. (C) CT at 15 days showed a large cerebral infarction on the contralateral side. (D) CT angiography on admission showed an aneurysm of the left ICA (arrow). (E) Digital subtraction angiography on day 8 showed severe vasospasm of the right MCA on the contralateral side (arrowheads).

large cerebral infarction on the contralateral side, whereas the ipsilateral MCA with NPRIs was not affected. Delayed cerebral infarction was prevented by NPRIs on the side of craniotomy, and a large infarction occurred on the contralateral side at which cerebral vasospasm was expected to be less likely.

DISCUSSION

We previously reported that vasospasm was completely prevented in the arteries of cisterns with thick clots, in which vasospasm was highly expected, by placing NPRIs adjacent to the arteries during surgery, without side effects.[2–4] However, efficacy was reduced for arteries remote from the placement of pellets because of the high lipophilicity of this drug. This local treatment targets a specific problem—that is, severe vasospasm. Our local treatment is based on the observation of Fisher *et al* that 'blood localized in the subarachnoid space in a sufficient amount at specific sites is the only important etiological factor in vasospasm'.[8]

In the present study, we confirmed the efficacy and safety of this local treatment: cerebral vasospasm and delayed cerebral infarction were both significantly less common in the NPRI group (p=0.004, OR=0.412 (95% CI 0.223 to 0.760) and p=0.005, OR=0.272 (95% CI 0.103 to 0.714), respectively). Different patterns were shown in outcomes at discharge between patients with SAH with and without NPRIs. This study has several potential limitations. Selection bias might have occurred. All patients in the NPRI group underwent craniotomy, whereas 88 patients in the non-NPRI group were treated by coil embolization. Furthermore, the timing of the judgment of outcomes was at discharge. Short-term outcomes in patients treated by a coil may be better than those treated by a clip because of the early adverse symptoms related to craniotomy.[7 9] Half of the patients with SAH belonged to WFNS grades 4 and 5 and the majority were Fisher group 3 in our critical center. In patients with severe grades, primary brain damage may be more closely related to the outcome than delayed cerebral infarction.

Although the findings of a randomized trial in a single institution were previously reported,[10] it is clear that a multicenter randomized control trial is needed for worldwide use. Since difficulties are associated with considering the adverse effects of local treatment of NPRIs at the time of placement, during elution, or the drug itself,[11] differences in outcomes may become clear in comparisons with patients treated by craniotomy. NPRIs have no adverse effects on additional treatments, such as decompressive surgery, hypertensive drug therapy, the severe management of volume, rescue therapy, and cerebrospinal fluid drainage. It is important to understand the efficacy and limitations of this local drug-delivery system.

CONCLUSION

NPRIs significantly reduced the occurrence of cerebral vasospasm and delayed cerebral infarction without any side effects. The NPRI and non-NPRI groups showed different patterns in short-term outcomes in the single critical care center, which may have been due to selection bias and patient characteristics. Differences in outcomes may become clear in comparisons of the NPRI and non-NPRI groups with a focus on patients treated by craniotomy.

Contributors Conception and design: HK. Acquisition of data: AS, HO, NA, YT. Analysis and interpretation of data: HO, NA, YT. Drafting the article: YK, HK. Critically revising the article: YK, SH. Reviewed submitted version of the manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: HK. Statistical analysis: YS. Drug supply: AF, TI. Study supervision: HK.

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