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AJNR Am J Neuroradiol 1985, 6 (6) 923-926
http://www.ajnr.org/content/6/6/923

Iohexol versus Metrizamide for Cervical Myelography: Double-Blind Trial

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Cervical myelography was performed by lateral C1–C2 puncture in 60 patients. Thirty patients received iohexol (an investigational aqueous contrast agent) and 30 received metrizamide in order to provide a prospective, randomized, double-blind trial comparing these contrast media. The two media produced radiographs of equal quality. Contrast-related morbidity was suffered by four patients (13%) in the iohexol group and by 11 patients (37%) in the metrizamide group. These features indicate that iohexol is superior to metrizamide as a contrast agent for cervical myelography.

Aqueous contrast materials have several well known advantages over oily and gaseous agents for myelography [1]. Metrizamide (Nyegaard, Oslo; Winthrop, New York City) has been considered the best one of the water-soluble contrast agents licensed for myelography by the Food and Drug Administration [2–6]. Metrizamide is highly hydrosoluble, mixes well with cerebrospinal fluid (CSF), and is absorbed relatively rapidly from the subarachnoid space without the need for aspiration of the agent at the conclusion of the examination [7]. Despite these advantages, troublesome qualities of metrizamide include high cost; an unwieldy stable state (lyophilized powder); and transient side effects such as headache, nausea, vomiting dizziness, meningeal irritation, fever, painful paresthesias in the legs, myoclonic leg spasms, seizures, confusion or other abnormal psychic states including hallucinations, affective lability, agitation, impaired memory, asterixis, global aphasia, and cortical blindness [1–5, 7].

Iohexol (N,N′-bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)acetamido]-2,4,6-triiodoisophthalamide) (Nyegaard, Oslo; Winthrop, New York City) is a more recently developed, investigational, water-soluble, nonionic, isotonic contrast medium that is chemically distinct from metrizamide but shares many of its favorable physical properties. Extensive laboratory investigations and clinical trials using iohexol for lumbar myelography indicate that iohexol appears to be superior to metrizamide for intrathecal application [7–12]. We report the results of a prospective randomized double-blind trial of iohexol versus metrizamide for clinical cervical myelography by lateral C1–C2 puncture.

Subjects and Methods

Sixty patients with appropriate clinical indications for cervical myelography participated in this study. Approval for conduct of the investigation was granted by the local institutional review board, and written informed consent was obtained from all patients. Exclusion criteria were age less than 18 years, pregnancy or lactation, emergency myelography, prior myelography or spinal operation or intrathecal chemotherapy within the preceding 1 month, spinal puncture during the preceding 48 hr, history of convulsive seizures or sensitivity to contrast media, concurrent participation in any other protocol for clinical investigation, and bloody CSF at the time of spinal puncture for myelography. Medications known to lower the seizure threshold were not permitted 48 hr before or after the myelography [4]. Examples include

Received October 11, 1984; accepted after revision January 22, 1985.

Presented at the annual meeting of the American Society of Neuroradiology, Boston, June 1984. (Preliminary results were presented at the annual meeting of the Radiological Society of North America, Chicago, November 1983.)

This work was supported by Sterling-Winthrop Research Institute, Rensselaer, NY.

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AJNR 6:923–926, November/December 1985
0195–6108/85/0606–0923

phenothiazine (prochlorperazine, chlorpromazine, etc.) and antidepressant drugs (amitriptyline, doxepin, etc.).

Clinical histories and extensive neurologic examinations with particular reference to vision, reflexes, motor function, and neuropsychiatric aberrations were obtained by a single physician (S. S. G.) within 24 hr before myelography and 4–6 hr as well as 24 hr after myelography. In cases of postmyelographic morbidity or alteration in neurologic findings on the 24-hr postmyelography evaluation compared with the premyelography status, further follow-up histories and examinations were obtained at 24-hr intervals (or more often) until the status of the patient returned to the premyelography state. The temperature, pulse, and blood pressure were monitored before, during, and after myelography.

Several serum chemistry and hematology parameters were examined within 4 hr before myelography and about 24 hr after myelography. The serum chemistry determinations were creatinine, BUN, albumin, total protein, alkaline phosphatase, and SGOT. The hematology parameters were hematocrit, hemoglobin, red and white blood cell counts, Westergren sedimentation rate, and platelet count.

A person who was not one of the investigators knew the secret code specifying the sequential order for administering metrizamide or iohexol. Either metrizamide or iohexol was administered intrathecally in a concentration of 300 mg I/ml. Whereas metrizamide must be stored in a lyophilized form and prepared as a solution shortly before its use, iohexol is stable in solution and can be autoclaved, distributed, and stored in a convenient, aseptic liquid state ready for immediate use. All the solutions were prepared blindly according to a computer-randomized code and handed to the radiologist in an unlabeled syringe containing 10 ml of contrast material. After removal of 2–10 ml of CSF for laboratory analysis, 5–10 ml of contrast material was injected at the rate of about 3 ml/min, often in fractions, with the aid of careful lateral fluoroscopic control of the cervical region and posterior cranial fossa to minimize intracranial spill of contrast medium. All clinical, laboratory, and myelographic findings were recorded before this code was broken to analyze the results.

Thirty patients received metrizamide and 30 received iohexol. Premyelographic medications (meperidine, secobarbital, and atropine) were administered intramuscularly to all patients, with doses varying according to body weight. Atropine was omitted if clinically contraindicated. While solid food was not permitted 8 hr before the myelogram, clear fluid oral hydration was encouraged. The strict "npo" status was specifically not permitted. All the myelograms were obtained by or under the supervision of a single neuroradiologist (S. S. G.). All spinal punctures were made by a lateral approach at the C1–C2 level with the patient prone, using a 20 or 22 gauge spinal needle, intradermal and subcutaneous 2% xylocaine anesthesia, and lateral fluoroscopic guidance. Frontal, lateral, and swimmers, and occasionally oblique views were obtained of the cervical and upper thoracic region with the patient prone. Although demonstration of the region of the foramen magnum including the cisterna magna was permitted during this trial, no deliberate attempt to direct any additional intracranial flow of contrast material was permitted. For imaging the region of the foramen magnum, 14 patients receiving metrizamide and 13 patients receiving iohexol were turned into the supine position for frontal and lateral filming at the end of the cervical myelography. Immediately after cervical myelography, several patients also underwent thoracic myelography in the supine position, and a few had lumbosacral myelography. At the end of the examination, the contrast material was pooled in the caudal sac by positioning the patient in a nearly upright position for about 5 min. Brief fluoroscopic examination of the cervical subarachnoid space was then performed to verify clearance of contrast material from this region.

After myelography, the patient was instructed to remain in a position of about 45° head elevation for 8 hr and, thereafter, maintain the head elevated about 20°–30° for another 8–10 hr. The patient was permitted to have bathroom privileges 8 hr after the examination but was instructed to otherwise remain in bed and as inactive as possible. Fluid intake was actively encouraged after myelography.

In seven patients receiving metrizamide and in 10 patients receiving iohexol, computed tomography (CT) was performed at intervals of 4–10 hr after myelography, as clinically indicated. Because CT necessitated placing the patient in the supine position, CT was delayed as long as possible after myelography without risking any compromise of the technical quality of the follow-up CT examination. However, strict care was exercised in moving the patient and keeping the head and neck as flexed and elevated as was technically feasible to minimize intracranial flow of contrast material.

All films were evaluated for technical and diagnostic quality by a single neuroradiologist (S. S. G.). Evaluation included demonstration of the spinal cord, root sleeves, individual nerve roots in the sleeves, and overall demonstration; each was scored as excellent, good, poor, or not imaged. Excellent demonstration provided more than sufficient information to make a myelographic diagnosis, good demonstration provided sufficient information, and poor demonstration did not provide sufficient information to make a myelographic diagnosis.

Results

All 30 myelograms obtained with metrizamide were judged to be of excellent technical quality. Of the iohexol group, 29 were judged to be excellent. One was judged to be good; this less-than-excellent demonstration in the lower cervical region resulted from an incomplete but severe myelographic block that necessitated marked fractionation of the injected contrast material to avoid excessive intracranial spill of the contrast material. Among patients having follow-up CT, there was no discernible difference in the technical quality of the CT images obtained in the iohexol and metrizamide groups.

In the iohexol group, there were 20 men (20–70 years) receiving 6–10 ml of contrast material and 10 women (30–58 years) receiving 7–10 ml of contrast material. In the metrizamide group, there were 16 men (21–66 years) receiving 5–10 ml of contrast material and 14 women (31–68 years) receiving 6–10 ml of contrast material.

In the iohexol group, 26 patients (87%) had no morbidity. One man developed mild "head fullness" (not a headache) and one woman developed transient, purely subjective leg weakness. One woman had a "trivial" headache and another woman had headache, nausea, and vomiting. The "trivial" headache had been present before myelography and did not change in intensity afterward. The incidence of headache was 7% and the incidence of nausea and vomiting was 3%.

In the metrizamide group, 19 patients (63%) suffered no morbidity. The following types of postmyelographic morbidity occurred: headache, nausea, and vomiting (one man, one woman); headache (four men); nausea and vomiting (two men, two women); and headache, nausea, vomiting, and transient leg weakness (one woman). The woman who developed transient leg weakness after myelography had marked cervical syringomyelia, with extensive uptake of contrast material within the syrinx cavity demonstrated on postmyelography CT. Tabulating the postmyelography morbidity in the metrizamide group in another manner, seven patients (five men, two women) (23%) developed headache and seven patients (three men, four women) (23%) had a combination of nausea and vomiting.

Five patients in the iohexol group and four patients in the metrizamide group had degenerative joint disease and spinal stenosis that caused varying degrees of obstruction to the caudad flow of contrast medium between the third and sixth cervical levels. One of these five iohexol patients reported "head fullness" after myelography and another suffered subjective transient leg weakness. Two of the four metrizamide patients suffered postmyelographic headache. As previously mentioned, all patients in our study were placed in the near-upright, supine position for about 5 min after completion of myelographic filming. Fluoroscopic examination of the cervical subarachnoid space after nearly upright positioning at the end of myelography showed no detectable contrast material in this region in any patient.

All postmyelography morbidity was transient, and no additional morbidity was reported or detected in any of the patients in either the metrizamide or iohexol group. Specifically, no patient developed seizures or other abnormal neurobehavioral or psychic states. There was also no significant change in vital signs during and after myelography as compared with before myelography. Likewise, there was no significant change in the serum chemistry or hematology parameters when comparing the values obtained before and after myelography in either the iohexol or metrizamide group.

The statistical significance for the difference in the incidence of lack of morbidity in the iohexol versus metrizamide groups showed a p value (chi-square analysis) of less than 0.025. The difference between the two groups with respect to the individual incidences of nausea and vomiting both showed a p value (Fisher exact test) of less than 0.05. The difference for headaches showed a p value (Fisher exact test) of less than 0.07. With the exclusion of the "trivial" headache, reasonable in light of the lack of change in this headache after myelography, the p value (Fisher exact test) is less than 0.05.

Discussion

Previous studies comparing iohexol with metrizamide for lumbar myelography demonstrated decreased frequency and severity of postmyelographic morbidity for iohexol [7, 9, 10]. Although the results of our own previous work showed less morbidity than reported by other authors with respect to both metrizamide and iohexol for lumbar myelography, there was still a significant difference between the two agents [9, 10]. In regard to headache, a p value of less than 0.025 was found in the lumbar study, whereas the present cervical study resulted in a p value of less than 0.05 (when the "trivial" headache is excluded). It is reasonable to expect greater flow of higher-concentration contrast material to enter the intracranial subarachnoid spaces during and after cervical rather than lumbar myelography. However, careful postmyelographic pooling of contrast material in the caudal sac may reduce the incidence and severity of the expected increased morbidity. This was suggested by the overall low incidence of morbidity in our previous lumbar (eight of 50 patients) [9, 10] and our present cervical (15 of 60 patients) studies where such techniques were strictly employed.

In our extensive experience with cervical myelography done by C1–C2 puncture, the development of motor weakness as an apparent complication of myelography is rare. The purely subjective transient leg weakness in one woman who received iohexol and the objective transient leg weakness in one woman who received metrizamide are of unknown etiology. Nevertheless, it is conceivable that the large amount of contrast material within the syrinx cavity somehow may have caused the transient postmyelography leg weakness that developed in the patient who received metrizamide in our present trial.

Cervical myelography usually requires the patient to assume the prone position, often with significant, lengthy extension of the head and neck. This results in buckling of the ligamenta flava and tends to aggravate any incomplete cervical myelographic block. Nine patients in our series had varying degrees of myelographic block due to cervical spondylosis and spinal stenosis. Four of them suffered some type of postmyelographic morbidity. As previously mentioned, all patients in our study had fluoroscopic verification of cervical subarachnoid space clearance of contrast material after the completion of myelographic filming, and there was a nearly equal number of patients with incomplete myelographic blocks in the metrizamide and iohexol groups. However, it is interesting to note that of the four iohexol patients with postmyelographic morbidity, two (50%) had some degree of myelographic block. This included the woman with transient subjective leg weakness.

Subpial or spinal medullary injection of contrast material may cause complications [13, 14]; however, none of our patients had radiographic evidence for such injection.

A significant incidence of morbidity, especially headache, may be expected after a lumbar puncture, even without intrathecal administration of any contrast material [5, 15, 16]. The role of the C1–C2 spinal puncture itself as a possible contributing factor to the types and incidences of postmyelography morbidity is purely speculative in the absence of any pertinent, controlled study. Nevertheless, the postmyelography morbidity in our investigation is remarkably low, at least with respect to the iohexol group.

The results of our current double-blind clinical trial confirm the findings of previous laboratory and clinical investigations [7–12] that a significant decrease in postmyelography morbidity may be expected with the use of iohexol as compared with metrizamide for cervical myelography, with no sacrifice in image quality.

ACKNOWLEDGMENT

We thank Sandra Ressler for assistance in manuscript preparation.

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