Evaluation the clinical effects of neuroleptanalgesia (Remifentanil-Acepromazine, Remifentanil-Xylazine, and Remifentanil-Midazolam) during intubation and some minor surgical operations in dogs

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Abstract

The present study intends to evaluate and compare the clinical effects of neuroleptanalgesia induced by using one of the sedative-opioid or tranquilizer-opioid (neuroleptanalgesia) combinations during intubation and some minor surgical operations in dogs. Twenty seven apparently healthy dogs weighing from (15-20 kg) and aged (2-4 years) were divided into three groups, all animals were premedicated with atropine (0.03 mg/kg BW) IM, after 15 minutes neuroleptanalgesia induced as following: Group 1, giving Acepromazine 1mg/kg BW IM and remifentanil 0.5 µg/kg BW IV. Group 2, giving Xylazine 2mg/kg BW IM and remifentanil 0.5 µg/kg BW IV. Group 3, giving Midazolam 0.2mg/kg BW IM and remifentanil 0.5 µg/kg BW IV), in 10 minutes interval respectively in all groups. The following parameters were used for evaluation during the state of (neuroleptanalgesia), eye reflexes, duration and degree of surgical analgesia, degree of sedation, muscle relaxation, respiratory rate, rectal body temperature, and heart rate and rhythm. The results of the study was characterized by good sedation with minor change in heart and respiratory rates and body temperature with excellent analgesia and muscle relaxation quite enough to performed intubation, docking and declawing in groups one and two and less in quality in third group. Neuroleptanalgesia programs in all groups are good for reduce fear and induce restraint necessary for diagnostic procedures, physical examination or some minor surgical operations.
Key words: Neuroleptanalgesia, remifentanil, acepromazine, xylazine, midazolam, dog.

تقييم التأثير السريري لحالة التسكين المقلدي المحدث في الكلاب باستخدام (الريمفنتانيل والاسيبرومازين ، الريمفنتانيل والزيلازين ، الريمفنتانيل والميدازولام) من خلال اجراء بعض العمليات الجراحية و ادخال انبوب الرغامى

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الخلاصة

اجريت هذه الدراسة لغرض تقييم ومقارنة التأثير السريري لحالة التسكين المقلدي المحدث باستخدام المسدرات ، المهدئات مع الافيونات من خلال اجراء بعض العمليات الجراحية البسيطة او ادخال انبوب الرغامي في الكلاب. استخدمت في التجربة سبعة وعشرين من الكلاب (والتي تبدوا معافات) يتراوح وزنها مابين (15-20 كغم) واعمارها مابين (2-4 سنوات) جرى اعطاءها الأتروبين (0.03 ملغ/كغم) قبل 15 دقيقة من اعطاء ادوية التسكين المقلدي . قسمت الحيوانات إلى ثلاث مجموعات: المجموعة 1، تم إعطاءها الاسيبرومازين 1 ملغ/كغم بالعضلة والريميفنتانيل 0.5 ميكروغرام/كغم من وزن الجسم وريديا. المجموعة 2، اعطيت الزيلازين 2 ملغ/كغم بالعضلة والريميفنتانيل 0.5 ميكروغرام/كغم من وزن الجسم وريديا. المجموعة 3، تم إعطاءها الميدازولام 0.2 ملغ/كغ والريميفنتانيل 0.5 ميكروغرام/كغم من وزن الجسم وريديا في فترة 10 دقائق على التوالي في جميع الفئات. تم استخدام المعلمات التالية لتقييم حالة التسكين المقلدي: منعكسات العين، مدة ودرجة التسكين الجراحي، درجة التسدير، استرخاء العضلات، ومعدل التنفس، ودرجة حرارة المستقيم ، معدل ضربات القلب. اظهرت النتائج حصول تسدير جيد مع تغير قليل في معدل التنفس ومعدل ضربات القلب ودرجة حرارة الجسم مع حصول تسكين وارتخاء عضلات ممتازين في المجموعتان الاولى والثانية كافيان لإدخال انبوب الرغامى

واجراء عملية ازالة الضفر وعملية بتر الذيل. اما المجموعة الثالثة كانت اقل في الجودة. نستنتج من هذا ان برامج التسكين المقلدي في جميع المجموعات كان جيدا لإزالة الخوف واحداث السيطرة اللازمة لإجراءات التشخيص و الفحوصات البدنية أو اجراء بعض العمليات الجراحية البسيطة.

الكلمات المفتاحية: التسكين المقلدي ، الريميفنتانيل ، الاسيبرومازين ، الزيلازين ، الميدازولام ، الكلاب.

Introduction

Remifentanil is a potent ultra-short acting synthetic opioid analgesic drug. (1). It is a recently developed full opioid agonist, which is now extensively used in human anesthesia, and has been the subject of research in veterinary anesthesia. It is given to patients during surgery to relieve pain and as an adjunct to an anesthetic. Remifentanil is used for sedation as well as combined with other medications for use in general anesthesia. Remifentanil administered either as a constant infusion, or as a PCA (patient controlled analgesia) system, or both is a very good alternative to Pethidine as an obstetric analgesic (2). The Mu-opioid activity of remifentanil is antagonized by naloxone. It is an ultra-short-acting agent of similar potency to fentanyl administered by intravenous infusion during surgery (3). The major advantage of remifentanil over fentanyl and alfentanil is that the drug is broken down by non-specific plasma and tissue esterase, and does not rely on metabolism and excretion by the liver and kidneys. Thus, there should be no cumulating in patients with hepatic or renal disease. Recovery from the effects of remifentanil occurs rapidly (within 5 to 10 minutes). New steady-state concentrations occur within 5 to 10 minutes after changes in infusion rate. When used as a component of an anesthetic technique, remifentanil can be rapidly titrated to the desired depth of anesthesia/analgesia (e.g., as required by varying levels of intraoperative stress) by changing the continuous infusion rate or by administering IV bolus injection (4). Xylazine is a potent sedative, analgesic and muscle relaxant drug in animals. It is a typical alpha-2 adrenoceptor agonist and exerts its effects most likely by activation of central presynaptic alpha 2- receptors in the brain. Activation of these central alpha2-receptors seems to regulate central dopamine norepinephrine storage or release (so sedation and analgesia occur), sedative and analgesic activity are related to CNS depression mediated by stimulation of central presynaptic α-2 adrenoceptors, resulting in inhibition of norepinephrine release from adrenergic nerve terminals, while the muscle-relaxant effect is due to inhibition of intranural transmission of impulses to the CNS) (5,6,7). Acepromazine is a phenothiazine neuroleptic agent. The primary desired effect for the use of acepromazine in veterinary medicine is its tranquilizing action. Additional pharmacologic actions that acepromazine possess, include antiemetic, antispasmodic, anticonvulsant and hypothermic actions. It may decrease respiratory rates, with little or no effect on the blood gas picture, pH or oxyhemoglobin saturation. A dose dependent decrease in hematocrit is seen within 30 minutes after dosing in the horse and the dog (8). Besides a lowering of arterial blood pressure in the dog, acepromazine causes an increase in central venous pressure, a vagally induced bradycardic effect and transient sinoatrial arrest (9). Acepromazine is approved for use in dogs, cats, and horses as an antiemetic and as a preanesthetic agent. Animals may require lower dosages of general anesthetics. The benzodiazepine group has been widely used in human and veterinary medicine applications. Midazolam is two times potent more than diazepam. It is considered to be fast acting with a short elimination half-life, it unlike diazepam can be administered by the intramuscular route as well as the intravenous route, and it has mild respiratory effects and is commonly used as a mild tranquillizer (10). The sedative and hypnotic effects of midazolam are dose-dependent as well as dependent on route of administration, midazolam can produce maximal sedative effects in 20 minutes after intramuscular administration of 0.6 mg/kg (11).

The anesthetist aims to prevent awareness of pain, provide immobility and, whenever this is needed, relaxation of the skeletal

muscles. These objectives must be achieved in such a way that the safety of the patient is not risked during the preoperative period. Many animals fear and resist the restraint necessary for the administration of drug, diagnostic procedures, physical examination or some minor surgical operations (12). This will increase not only the technical difficulties of such procedures but also the dangers inseparable from their use. To sedate an animal that is in pain a suitable analgesic must be used, possibly in combination with a sedative drug, because most sedative drugs themselves have little or no analgesic activity and may cause exaggerated reactions to painful stimulation. Sedative-opioid or tranquilizer-opioid combinations (neuroleptanalgesia) are used for procedures such as radiography, examinations, bandage changes and minor orthopedic manipulations, and for preanesthetic medication (13). The combination of an opioid with a sedative may accomplish one of two goals. One is to increase the degree of sedation and analgesia beyond that achieved by use of the sedative or opioid alone. The second, the combination allows a decrease in dose rate of one or both of the drugs while still achieving satisfactory sedation. Decreased dose rates may result in less respiratory or cardiovascular depression, less airway obstruction in brachycephalic breed dogs, and less drug to be metabolized for recovery. For these reasons the study intends to evaluate and compare the clinical effects of neuroleptanalgesia induce by using one of the sedative-opioid or tranquilizer-opioid combinations (neuroleptanalgesia) during intubation and some miner surgical operations in dogs.

Materials and methods

The study was conducted on twenty seven apparently healthy dogs weighing (15-20 kg) and aged (2-4 years). Intravenous cannula was fixed in the cephalic vein after fasting of animal 12 hrs. prior giving the drugs to facilitate drug administration. Atropine sulfate (0.03 mg/kg BW) IM were given 15 minutes before neuroleptic drug administration. Animals were divided into three groups. G1 was giving acepromazine 1mg /kg BW IM, and remifentanil 0.5 µg/kg BW IV. G2 was giving xylazine 2mg /kg BW IM and remifentanil 0.5 µg/kg BW IV. G3 was giving midazolam 0.2mg /kg BW IM, and remifentanil 0.5 µg/kg BW IV in 10-min intervals respectively in all groups. The respiratory rate, heart rate, rectal temperature, degree of analgesia (by pin prick), muscle relaxation, eye reflexes were taken before giving the drugs and consider as control reading, then same reading were taken every 5minutes for one hour. The recovery periods also recorded. The quality and duration of neuroleptanalgesia, endotracheal intubation and some miner surgical operations, like docking, amputation of first digit in some animals were done to evaluate the efficacy of the neuroleptanagesic protocols.

Statistical analysis

Data were expressed as mean ± standard error and had been analyzed by using Analysis of Variance (ANOVA) and Least Significant Differences (LSD) to compare between groups, (P=Value) (14).

Results

The degree of sedation in G1 and G2 was expressed as deep sedation, and the animals were seen depressed, drowsy and sleepy, with attain to sternal recumbence and no resistance to positioning on lateral recumbency. In G3 animals were seen slightly sedated, mild signs of depression, drowsiness or ataxia with diminution the reaction to external stimuli. The heart rate was started increased in all groups from the first five minutes and show significant deference between control time with 10, 15, 20, 25, 30, 45and 60 min. after the injection of xylazine, midazolam, and acepromazine then continues increased and stable above base line to the end of experiment (Table 1). The respiratory rate was gradually decreased during the first ten minutes in all groups and show significant deference between control time and 10, 15, 20, 25, 30, 45 and, 60 min. The decreased after the injection of xylazine, then continues clearly decreased after

Table (1): The effects of different neuroleptianalgesic protocols on heart rate (beats/min) in dogs.

Groups	Time minutes												
	Zero	5	10	15	20	25	30	35	40	45	50	55	60
G1	78.5 ± 0.68 h	79.9 ± 1.36 h	87.3 ± 1.98 A gh	91.3 ± 2.18 A fg	95.8 ± 1.94 A ef	98 ± 1.52 A ef	103.8 ± 2.32 de	107.5 ± 2.57 cd	111.5 ± 2.56 bsd	114.9 ± 3.04 abc	118.7 ± 3.35 ab	123 ± 2.99 ab	124.8 ± 2.98 AB a
G2	74.3± 2.08 i	74.3± 2.08 i	84.3± 2.91 AB h	89± 3 AB h	90.4± 3.77AB gh	96.8± 77 AB fgh	102± 4 ef	106.2± 4.1 de	112.2± 2.96 cd	117.3± 3.83 dc	121.3± 3.96 b	124.5± 32.82 ab	130.8± 2.56 AB a
G3	71.2± 2.58 j	72± 2.36 j	77.9± 2.68 B ij	84± 2.22 B hi	87.4± 2.94 B gh	90.3± 2.88 B fgh	97.3± 2.44 ef	101.4± 2.83 de	106.1± 3.22 cd	110.3± 3.33 bc	114.2± 3.50 abc	117.6± 2.91 ab	120.8± 3.15 B a

G1: Atropine, xylazine and Remifentanil, G2: Atropine, midazolam and Remifentanil, G3: Atropine, Acepromazine and Remifentanil. Capital latters revealed those significant differences at the level (p< 0.005) among times. Small latters revealed that significant differences at the level (p< 0.005) among groups.

Table (2): The effects of different neuroleptianalgesic protocols on respiratory rate (breath/min) in dogs.

Groups	Time Zero X± SE	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.	55 min.	60 min.
G1	a	ab	ab	bc	cd	cde	def	efg	fg	gh	hi	i	i
	25.33 ±0.33	B 24.44 ±0.66	23.66 ±0.68	22.66 ±0.5	21.44 ±0.81	21 ±0.86	20.2 ±0.93	19.1 ±1.04	18.22 ±0.91	17.66 ±1.04	16.11 ±0.82	15.5 ±0.71	15.1 ±0.71
G2	a	a	ab	abc	abe	be	cde	de	efg	fg	gh	hi	i
	25.3 ±0.33	AB 25.33 ±0.33	24.3 ±0.37	23.5 ±0.37	23.3 ±0.5	22.78 ±0.40	21.89 ±0.51	20.78 ±0.62	20 ±0.58	18.78 ±0.66	17.67 ±0.82	16.44 ±1.30	15.56 ±0.62
G3	a	a	b	bc	cd	cd	de	e	ef	f	g	g	g
	27.11 ±1.11	A 27.11 ±1.11	24 ±0.41	23.22 ±0.66	22.22 ±0.82	21.78 ±0.86	20.78 ±0.86	19.67 ±1.1	19.11 ±0.99	17.67 ±1.0	15.67 ±0.67	15.56 ±0.62	14.22 ±0.36

G1: Atropine, xylazine and Remifentanil, G2: Atropine, midazolam and Remifentanil, G3: Atropine, Acepromazine and Remifentanil. Different capital letters demonstrate significant difference, different small letters horizontally demonstrate significance among times in same group.

Table (3): The effects of different neuroleptianalgesic protocols on rectal temperature (C˚) in dogs.

Time / Group	Zero X± SE	5 min.	10 min.	15 min.	20 min.	25 min.	30 min.	35 min.	40 min.	45 min.	50 min.	55 min.	60 min.
G1	a	ab	ab	b	bc	bcd	cd	def	defg	efg	fg	g	g
	37.71 ±0.06	37.54 ±0.10	37.41 ±0.10	37.23 ±0.08	C 37.10 ±1.41	37.03 ±0.1	36.86 ±0,10	36.67 ±0.13	36.58 ±0.08	36.42 ±0.11	36.32 ±0.10	36.24 ±0.06	36.16 ±0.05
G2	a	a	a	ab	be	be	Cd	cde	def	efg	f	gi	j
	37.43 ±0.12	37.42 ±0.11	37.2 ±0.10	37.05 ±0.13	B 36.84 ±0.15	36.82 ±0.11	36.68 ±0.12	36.61 ±0.12	36.38 ±0.09	36.3 ±0.06	36.22 ±0.07	36.11 ±0.05	36.88 ±0.04
G3	a	a	abc	bc	cd	de	ef	ef	fg	gh	hi	hi	i
	37.6 ±0.12	37.52 ±0.11	37.37 ±0.09	37.15 ±0.10	A 37.12 ±0.13	36.96 ±0.13	36.73 ±0.12	36.7 ±0.13	36.56 ±0.15	36.44 ±0.10	36.22 ±0.06	36.17 ±0.05	36.13 ±0.03

G1: Atropine, xylazine and Remifentanil, G2: Atropine, midazolam and Remifentanil, G3: Atropine, Acepromazine and Remifentanil. Different capital letters demonstrate significant difference, different small letters horizontally demonstrate significance among times in same group.

injection of remifetanil and stable above base line to the end of experiment. However, no signs of apnea or cyanotic mucous membranes were observed in any of the dogs in all groups (Table 2). Body temperature was gradually reduced in all animals of the three groups (Table 3). Deep analgesia (DA) was extend from 30 min to 55 min in G1, from35 min to 50 min in G2, and from 45 min to 55 min in G3 (Table 4). The degree of muscle relaxation in G1 and G2 started early after the animals premeditated with xylazine in G1and midazolam in G 2 and reach to the optimum degree and extending to 60 min. time of observation (Table 5). The palpebral and corneal reflexes in neuroleptanalgesic groups were never abolished completely, it become nearly sluggish at time 35 min. in G1. The pupil size reflex was found contracted in all groups.

Table (4): The effects of different neuroleptianalgesic protocols on analgesia in dogs

Time / Groups	Zero	5m	10m	15m	20m	25m	30m	35m	40m	45m	50m	55m	60m
G1	NA	NA	NA	NA	LA	MA	DA	DA	DA	DA	DA	DA	MA
G2	NA	NA	NA	NA	NA	NA	MA	DA	DA	DA	DA	MA	LA
G3	NA	NA	NA	NA	NA	NA	NA	NA	LA	MA	MA	MA	LA

G1: Atropine, xylazine and Remifentanil, G2: Atropine, midazolam and Remifentanil, G3: Atropine, Acepromazine and Remifentanil. NA =No analgesia, LA =Light analgesia, MD=Mild analgesia, DA=Deep analgesia.

Table (5): The effects of different neuroleptianalgesic protocols on degree of muscle relaxation in dogs.

Time / Groups	Zero	5m	10m	15m	20m	25m	30m	35m	40m	45m	50m	55m	60m
G1	NR	NR	NR	NR	LR	MR	DR	DR	DR	DR	DR	DR	MR
G2	NR	NR	NR	NR	NR	NR	MR	DR	DR	DR	DR	MR	LR
G3	NR	NR	NR	NR	NR	NR	NR	NR	MR	LR	LR	LR	LR

G1: Atropine, xylazine and Remifentanil, G2: Atropine, midazolam and Remifentanil, G3: Atropine, Acepromazine and Remifentanil. NR=No relaxation, LR =Light relaxation, MR=Mild relaxation, DR=Deep relaxation.

Discussion

The concept of neuroleptanalgesia involves the combination of a neuroleptic agent (Alpha 2 adrenoceptor agonist, benzodiazepines, or phenothiazines) with a potent opioid, when combined a state of "neuroleptic-analgesia" may be produced in which the patient lies at rest and is completely passive. When sedatives of any of the three major groups are combined with opioids, the sedative effect is synergistic. The degree of sedation, as judged by lack of response to stimulation, being greater than the additive effect (15). The result of sedation in two groups (xylazine and midazolam groups) was seen deep. Benzodiazepines cause retrograde amnesia when used on their own, but can be act as depressant in various combinations. Alpha 2 agonist and opioid combination shows marked synergism, it is possible to obtain all degrees of sedation and, in some cases, anesthesia with such combinations. Alpha 2 adrenoceptor effects are numerous positive effects are sedation and analgesia (16). In acepromazine group the sedation was mild. Phenothiazines calm the animal and in some individuals may make them sleepy, but however higher dose causes hypnosis and deep sedation achieved when combined with opioids, the sedative effect of opioids is synergistic the degree of calamines of phenothiazine lead to lack of response to stimulation, being greater than alone effect. (17). The heart rate was seen elevated during the time of observation till the end of experiment. The anticholinergic have been used to prevent bradycardia caused by administration of different sedatives in dogs.

Atropine inhibits the action of acetylcholine on the muscarinic cholinergic receptors and would be a drug of choice when severe bradycardia is presented secondary to increased vagal tone (18, 19). Administration of the acepromazine or xylazine combination with other sedative or narcotic analgesic at very high doses resulted in a slight, insignificant increase in heart rate in dogs premedicated with atropine (20). The combined effects of atropine and acepromazine increases in heart rate may be observed in some animals following IV administration of acepromazine in response to peripheral vasodilation (21, 22). The effects such combinations on cardiovascular system are very variable depending on the species, drug, rout of administration, and type of preparation. All drugs of the neuroleptic-analgesic cause centrally-mediated cardiovascular effects causing inhibition of sympathetic tone to the heart, but the effect are completely differ when such drugs are used alone or as a part of anesthetic protocol (23). Tachycardia are observed following injection of neuroleptic-analgesia combination in this study may be attributed to premedication with Atropine sulfate which block transmission at parasympathetic postganglionic nerve endings and block the effects of impulses in the vagal nerves and prevents bradycardia associated with intravenous administration of the potent neuroleptic-analgesia (24). The respiratory rate was seen gradually decrease during the first ten minutes in all groups and show significant deference compared with control. The decreased respiratory rate may be attributable to sedation and reduced anxiety. In remifentanil group, the depression more clear may be due the depression effect of this drug (25, 26). The most prominent effect on respiration was seen attributed to the opioid constituent. Generally opioid (naturally and synthetic) causes respiratory depression by inhibition of the brain-stem respiratory center. Sedation with alpha 2-agonist result in a reduction in respiratory rate for varying periods. Respiratory depression occur secondary to the C.N.S depression produced by alpha 2-adrenoreceptor stimulation; however the degree of depression with alpha 2-agonists alone is less than that with other sedative (27). In all animals of the three groups there was gradual decrease in body temperature. The administration of sedatives and tranquilizers generally depress the basal metabolic rate and induce muscle relaxation, resulting in lowered body temperature (22). Phenothiazines cause peripheral vasodilation, which may exaggerate hypothermia (5). Hypothermia may be much more profound in smaller patients due to their larger body surface area to body mass ratio. The hypothalamic thermoregulatory center is also affected by phenothiazine administration, leading to the loss of thermoregulatory control. The hypothermic effects of α2-agonists are mediated by activation of the α2 C receptor subtype (22). However, α2-agonists may reduce cutaneous heat losses by peripheral vasoconstriction and central redistribution of blood, resulting in preservation of body temperature. Deep analgesia was gained from 30 to 55 minutes in G1, from 35 to 50 minutes in G2, and from 45 to 55 minutes in G3. The analgesic effect of our combination was mediated through alpha 2-agonists drugs. Xylazine is a potent analgesic for certain types of pain. Analgesic activity are related to CNS depression mediated by stimulation of central presynaptic α-2 adrenoceptors, resulting in inhibition of norepinephrine release from adrenergic nerve terminals (28, 29). Xylazine combined with an anesthetic drugs result in a synergistic effect, extending both the duration and potency of the total analgesic effect (30). Opioids dampen peripheral and central afferent nociceptive receptors. It produce analgesia by binding to either mu, K or sigma receptors located within the CNS, either spinally or supraspinally, although many suggestions that opioid analgesia can be brought about by activation of opioid receptors located peripherally in inflamed tissues has gained more acceptance (31). All opioid drugs displaying agonist activity at mu receptors are analgesics. Acepromazine group in the present study give the least time of analgesia. Acepromazine is the most common phenothiazine used in small animals this drug generally provides excellent

sedation but provides no analgesia on its own. However, acepromazine can enhance the effects of analgesic drugs when co-administered. The degree of muscle relaxation started early in two groups after the animals premedicated with xylazine in G1 and midazolam in G2 which reached to the optimum degree extending to 60 minutes. Generally muscle relaxation produce by benzodiazepines is probably mostly central in origin although some of this action is also attributable to direct activity at the postsynaptic neuromuscular junction and cause depression of musculoskeletal reflexes (32). The muscle-relaxant effect of xylazine is by the inhibition at the alpha 2-adrenoreceptor at the interneuron of the spinal cord and inhibition of intranural transmission of impulses to the CNS (5). The palpebral and corneal reflexes were never abolished completely in the three neuroleptanalgesic protocols, it become nearly sluggish at time 35 minute in G1.The palpebral and corneal reflexes were difficult to suppress these reflexes may be consistently abolished only immediately before fatal respiratory arrest (15). The pupil size reflex was found contracted in all neuroleptanalgesic groups this may be due to the presence of opioid substitute in the combination of mixtures. Miosis is often considered an effect of opioid administration during anesthesia (33, 34) Remifentanyl induce miosis and impairment of extra ocular muscle control (35). Mydriasis is commonly observed after xylazine administration, this effect is caused by central inhibition of parasympathetic tone to the iris and/or direct sympathetic stimulation of alpha-2 adrenoceptors located in iris and CNS (30).

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