Clinical trial results:
Systemic hypotension following intravenous administration of contrast medium during computed tomography.

Summary

EudraCT number	2013-002051-15
Trial protocol	AT
Global end of trial date	22 July 2015

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	KM-HYPO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52 A, Innsbruck, Austria, 6020
Public contact	Priv.Doz. Dr. Mag. Gerlig Widmann, Innsbruck Medical University, Department of Radiology, Section of Microinvasive Therapy, +43 (0)51250422761, gerlig.widmann@i-med.ac.at
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2015
Global end of trial reached?	Yes
Global end of trial date	22 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary goal of this study is to quantify changes in systolic and diastolic blood pressure, heart rate and pO2 before and after i.v. administration of either IOCM or LOCM. In particular the occurrence of clinically relevant drops in systolic and diastolic blood pressure after IOCM or LOCM administration is investigated.

Protection of trial subjects:

If sudden undesired clinical relevant events occur during the infusion of the study drug, the infusion should be stopped immediately and the events have to be treated properly. Very rarely, allergic reactions may occur. In case of severe skin rashes, angioedema, and/or bronchospasm, combined with tachycardia and hypotension and unexplained by other causes, infusion will be stopped and treatment will be implemented immediately. If thrombembolism to pulmonary, cerebral, coronary arteries or to other organs is diagnosed (CT scan, ECG, Echocardiography). Individually appropri-ate treatment will be implemented immediately.

Background therapy:

Basically all patients were hydrated with crystalloid solution at a rate of 3-5 ml/kg body weight (250–500 mL) per hour during general anesthesia.
Administration of vasopressors during the procedure was documented.
All patients received oral premedication with midazolam (Dormicum; Roche Pharmaceutics) 30 minutes prior to intervention at doses between 3.75 and 7.5 mg.

Evidence for comparator:

LOCM (low-osmolar contrast medium) was reported to significantly decrease average renal blood flow and affect heart rate and left ventricular end-diastolic pressure during coronary ventriculography and angiography. In this trial IOCM (iso-osmolar contrast medium) iodixanol and LOCM iopromide, both FDA appoved, were compared to systematically quantify the hemodynamic effects of intravenous CM (contrast medium) application in patients under general anesthesia with continuous invasive blood pressure monitoring.

Actual start date of recruitment	27 October 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	19
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients having both radiological interventions with CM and continuous blood pressure measurement during general anesthesia were within the sampling frame of our study population. Consequently, we focused on patients with liver tumors undergoing RFA, in whom invasive blood pressure is measured routinely at our institution.

Pre-assignment

Screening details:

During November 18, 2014, and May 5, 2015, 50 patients were consecutively screened for eligibility, 40 of whom (20 LOCM, 20 IOCM) were included in the study. Eight patients were excluded by the exclusion criteria and 2 patients because the procedure could not be performed.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Blinding implementation details:

The 2 different CMs to which individual patients were assigned were determined with a randomized schedule. Allocation ratio was 1:1. The randomization list was generated independently by the clinical investigator and sent to the staff responsible for labeling the IMPs. The randomization list was kept confidential and consulted only by the principal investigator for assignment on the day of treatment. Patients and anesthesiologists were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iopromide

Arm description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. LOCM iopromide was used for this procedure.

Arm type	Active comparator
Investigational medicinal product name	Iopromide
Investigational medicinal product code	
Other name	Ultravist 370 mg I/mL
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

We used LOCM iopromide (Ultravist 370 mg I/mL; Bayer Austria Ges.m.b.H., Vienna, Austria) for contrast enhancement.
CM was administered using an automatic injector at a flow of 3 mL/s via a separate peripheral temporary venous catheter with single access using 80–150 mL (2× bodyweight, minimum 80 mL, maximum 150 mL). For each patient, normal saline solution (NSS) was administered by automatic injector during the nonenhanced CT scan as a placebo control using exactly the same dose and injection rate as the previously given CM.

Arm title	Iodixanol

Arm description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. IOCM iodixanol was used for this procedure.

Arm type	Active comparator
Investigational medicinal product name	Iodixanol
Investigational medicinal product code	
Other name	Visipaque 320 mg I/mL
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

We used IOCM iodixanol (Visipaque 320 mg I/mL; GE Healthcare Handels GmbH, Vienna, Austria) for contrast enhancement.
CM was administered using an automatic injector at a flow of 3 mL/s via a separate peripheral temporary venous catheter with single access using 80–150 mL (2× bodyweight, minimum 80 mL, maximum 150 mL). For each patient, normal saline solution (NSS) was administered by automatic injector during the nonenhanced CT scan as a placebo control using exactly the same dose and injection rate as the previously given CM.

Number of subjects in period 1	Iopromide	Iodixanol
Started	20	20
Completed	20	20

Period 2

Period 2 title	Follow-up period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The 2 different CMs to which individual patients were assigned were determined with a randomized schedule. Allocation ratio was 1:1. The randomization list was generated independently by the clinical investigator and sent to the staff responsible for labeling the IMPs. The randomization list was kept confidential and consulted only by the principal investigator for assignment on the day of treatment. Patients and anesthesiologists were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iopromide

Arm description:

Follow-up ended after completion of the study 30 days after inclusion into the study. In this time SAEs were evaluated.

Arm type	Active comparator
Investigational medicinal product name	Iopromide
Investigational medicinal product code	
Other name	Ultravist 370 mg I/mL
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

We used LOCM iopromide (Ultravist 370 mg I/mL; Bayer Austria Ges.m.b.H., Vienna, Austria) for contrast enhancement.
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Arm title	Iodixanol

Arm description:

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Arm type	Active comparator
Investigational medicinal product name	Iodixanol
Investigational medicinal product code	
Other name	Visipaque 320 mg I/mL
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

We used IOCM iodixanol (Visipaque 320 mg I/mL; GE Healthcare Handels GmbH, Vienna, Austria) for contrast enhancement.
CM was administered using an automatic injector at a flow of 3 mL/s via a separate peripheral temporary venous catheter with single access using 80–150 mL (2× bodyweight, minimum 80 mL, maximum 150 mL). For each patient, normal saline solution (NSS) was administered by automatic injector during the nonenhanced CT scan as a placebo control using exactly the same dose and injection rate as the previously given CM.

Number of subjects in period 2	Iopromide	Iodixanol
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups	
Reporting group title	Iopromide
Reporting group description:	
The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. LOCM iopromide was used for this procedure.	
Reporting group title	Iodixanol
Reporting group description:	
The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. IOCM iodixanol was used for this procedure.	

Reporting group values	Iopromide	Iodixanol	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	10	19
From 65-84 years	11	10	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.5	61.1	
standard deviation	± 10.3	± 12.4	-
Gender categorical Units: Subjects			
Female	7	9	16
Male	13	11	24

End points

End points reporting groups

Reporting group title	Iopromide

Reporting group description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. LOCM iopromide was used for this procedure.

Reporting group title	Iodixanol

Reporting group description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. IOCM iodixanol was used for this procedure.

Reporting group title	Iopromide

Reporting group description:

Follow-up ended after completion of the study 30 days after inclusion into the study. In this time SAEs were evaluated.

Reporting group title	Iodixanol

Reporting group description:

Follow-up ended after completion of the study 30 days after inclusion into the study. In this time SAEs were evaluated.

Primary: Systolic blood pressure

End point title	Systolic blood pressure

End point description:

After administration of CM systemic blood pressure showed a typical hemodynamic temporal course. Compared to the initial value obtained 1 minute before administration, systemic blood pressure first showed a slight increase, followed by a variable decrease and after 3 minutes recovery to initial and compensatory levels higher than initial. We did not alter the infusion or administer additional vasopressors so as to not skew the data.
Time from onset of decline in blood pressure to normotension was 105 ± 61 seconds (range, 25–300 seconds) for LOCM and 112 ± 20
seconds (range, 90–145 seconds) for IOCM.

End point type	Primary

End point timeframe:

Day 2

End point values	Iopromide	Iodixanol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mm Hg				
arithmetic mean (standard deviation)	78.57 (± 19.934)	119 (± 15.492)		

Statistical analyses

Statistical analysis title	Systemic hypotension
Comparison groups	Iodixanol v Iopromide
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Primary: Diastolic blood pressure

End point title	Diastolic blood pressure

End point description:

After administration of CM systemic blood pressure showed a typical hemodynamic temporal course. Compared to the initial value obtained 1 minute before administration, systemic blood pressure first showed a slight increase, followed by a variable decrease and after 3 minutes recovery to initial and compensatory levels higher than initial. We did not alter the infusion or administer additional vasopressors so as to not skew the data.
Time from onset of decline in blood pressure to normotension was 105 ± 61 seconds (range, 25–300 seconds) for LOCM and 112 ± 20
seconds (range, 90–145 seconds) for IOCM.

End point type	Primary

End point timeframe:

Day 2

End point values	Iopromide	Iodixanol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mm Hg				
arithmetic mean (standard deviation)	43.14 (± 8.946)	61.86 (± 7.330)		

Statistical analyses

Statistical analysis title	Systemic hypotension
Comparison groups	Iopromide v Iodixanol
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided

Primary: Heart rate

End point title	Heart rate

End point description:

Administration of CM was associated with an increase of heart rate measured during the lowest value of systemic blood pressure.

End point type	Primary

End point timeframe:

Day 2

End point values	Iopromide	Iodixanol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: bpm				
arithmetic mean (standard deviation)	62.9 (± 11.7)	55.7 (± 10.3)		

Statistical analyses

Statistical analysis title	Influence of CM on heart rate
Comparison groups	Iopromide v Iodixanol
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.042
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 2- day 30

Adverse event reporting additional description:

No suspected expected SAEs (SESAEs) and suspected unexpected SAEs (SUSAEs) were ob-served during treatment and follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Iopromide

Reporting group description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. LOCM iopromide was used for this procedure.

Reporting group title	Iodixanol

Reporting group description:

The intervention during which the study data were obtained followed the standard protocol for stereotactic radiofrequency ablation (SRFA). The SRFA procedure is performed in anesthetized patients in whom a CM-enhanced CT scan is required for planning of the ablation, a nonenhanced CT scan is obtained for verification of proper needle placement, and after ablation another CM-enhanced CT scan is performed for final verification of ablation size. IOCM iodixanol was used for this procedure.

Serious adverse events	Iopromide	Iodixanol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Iopromide	Iodixanol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	2 / 20 (10.00%)	
Injury, poisoning and procedural complications			
Perihepatic bleeding			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	

Hepatic bleeding subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28806208