FINAL REPORT: Study to assess the optimum dose of intravenous adenosine in the assessment of fractional flow reserve

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Abstract

Background

Adenosine is the most commonly used pharmacological agent used to measure the fractional flow reserve of angiographically intermediate coronary lesions. The most common dose used is 140 micrograms/kg/minute to achieve steady state hyperaemia. However, the data to support this dosing regimen is limited.

Methods

In a randomised controlled trial of 57 patients with angiographically intermediate lesions, we set out to compare the effects of administration of two separate higher-rate infusion rates of adenosine (180 micrograms/kg/min and 200 micrograms/kg/min) with standard dose adenosine infusion (140 micrograms/kg/min). The primary endpoint was to determine whether there was a statistically significant difference in fractional flow reserve after administration of a higher infusion rate. Secondary endpoints were to determine whether therapy would be altered as a result of a higher dose infusion and adverse events in response to high dose adenosine.

Results

A total of 57 patients were randomised to receive one of three regimes (n=19 in each group), which involved two infusions of adenosine of two minutes duration to achieve steady state hyperaemia as follows: (1) received infusion of 140 micrograms/kg/min followed by 140 micrograms/kg/min, (2) 140 micrograms/kg/min followed by 180 micrograms/kg/min, (3) 140 micrograms/kg/min followed by 200 micrograms/kg/min. The mean age of the patients was 60.6 years (+/-10). 34 lesions interrogated were in the left anterior descending artery, 10 right coronary artery, 10 circumflex, 1 left main stem, 1 saphenous vein graft to diagonal artery and 1 diagonal. Infusion of 180 micrograms/kg did not result in a significant change in Fractional Flow Reserve (FFR) from the standard regimen, nor did any patient's result change from non-significant. In the group receiving 200 micrograms/kg/min three patients (15.8%) had a change in FFR which would alter the result from being negative to positive (i.e. from non-flow limiting to flow limiting).

Introduction

Measurement of fractional flow reserve is a well validated method used to determine the haemodynamic significance of coronary lesions of intermediate severity. Use of this technology as a guide to PCI (Percutaneous Coronary Intervention) has been shown to result in reduced rates of

repeat urgent revascularisation at five years (1). In order to achieve maximal hyperaemia of the myocardium, vasodilator agents are used. By far the most widely used is the purine nucleoside adenosine. This has been administered in a variety of ways in the published literature- by intracoronary bolus, intracoronary infusion and most commonly, by intravenous infusion. Initial data from Wilson et al (2) demonstrated that intravenous infusion of adenosine at a dose of 140 micrograms/kg/minute for a period of 2 minutes resulted in 83% of the vasodilation achieved with intracoronary papaverine. Intracoronary adenosine given at a variety of doses fails to produce full hyperaemia. There has been only been one very small trial to study higher doses of adenosine comparing smokers and non-smokers (3). This had only 4 patients in each group.

Study aim

We aimed to assess in a randomised controlled clinical trial whether administration of a high dose regimen of adenosine to patients undergoing pressure wire assessment of intermediate coronary lesions, resulted in a statistically significant change in the fractional flow reserve in comparison to the standard dose adenosine regimen of 140 micrograms/kg/min.

Primary Outcome Measure

To compare the fractional flow reserve observed by administration of adenosine at both 180 micrograms/kg/min and 200 micrograms/kg/min with that achieved by administration of the standard dose of 140 micrograms/kg/ minute.

Secondary Outcome Measure

To compare the frequency of adverse events occurring due to administration of adenosine at each dose.

Methods

Full permission to undertake the study was obtained from a local Research Ethics Committee, the Medicines and Healthcare Products Regulatory Agency (MHRA) and the participating NHS organisation. The trial was registered on the European Clinical Trials database (EudraCT) as the protocol was a clinical trial of an investigational medicinal product (CTIMP). The study was carried out in one single site: Central Manchester University Hospitals NHS Foundation Trust. All patients provided full informed consent prior to participation. Patients were screened when they attended the pre-assessment clinic or when they arrived on the cardiac short stay unit, and a patient information sheet was provided to them. If they met the inclusion criteria and agreed to take part full consent was obtained. If angiographic findings warranted pressure wire study, they were randomly allocated to receive one of the three treatment allocations as follows:

(1) 140 micrograms/kg/minute of adenosine followed by another infusion of 140micrograms/kg/minute
(2) 140 micrograms/kg/minute of adenosine followed by another infusion of 180micrograms/kg/minute
(3) 140 micrograms/kg/minute of adenosine followed by another infusion of 200micrograms/kg/minute

Baseline demographics were recorded, including age, gender, smoking status, diagnosis of diabetes, prior myocardial infarction, documented left ventricular dysfunction. Haemodynamic parameters were recorded continuously prior to and during both infusions, as well as the baseline and minimum fractional flow reserve (FFR) recorded at maximum hyperaemia.

A 6F sheath was used to engage the coronary artery being studied. Adenosine was administered (at operator's discretion) either by a femoral venous sheath or by a large >18G cannula in an antecubital vein. Patients were anti-coagulated with 70u/kg of unfractionated heparin as per usual practice. The Radi pressure wire system was used (Uppsala, Sweden) as previously described (4). Care was taken to ensure that there was no damping of coronary pressure due to guide catheter. Prior to insertion of the pressure sensitive wire, it was flushed and laid flat at heart level. The wire was then calibrated, inserted through the guide catheter and positioned in the vessel proximal to the lesion of interest. At this point the wire was equalised as per protocol. The wire was then positioned distal to the lesion and the baseline FFR recorded. Adenosine was then infused according to the study protocol.

Statistics: Data was analysed using PASW Statistics version 18 and was expressed as mean (+/- standard deviation). A univariate analysis model was used to detect a statistical difference in the FFR level by comparing FFR at baseline to the FFR achieved after infusion of adenosine. Statistical significance was deemed to have been achieved when $p<0.05$.

Results

57 patients were recruited, of whom 47 (82%) were male. Mean age was 60.6 years (+/-10). Fifty-one (89%) of procedures were carried out on an elective basis, the remainder (11%) were stable acute coronary syndrome presentations. Fifteen patients (26%) were diabetic, 25 (44%) had hypertension, 34 (59.6%) had a positive family history of ischaemic heart disease, 26 (45.6%) were current smokers, 8 (14%) had documented left ventricular dysfunction and 42 (73.6%) had a history of previous myocardial infarction. One patient, initially randomised to receive 140 followed by 180 dose was removed from the study after developing transient heart block after the 140 microgram/kg/min dose of adenosine - this was determined to be an adverse reaction. For safety reasons the second dose was not administered. No other significant adverse effects were observed.

	Group 1	Group 2	Group 3	Overall
N	19	19	19	57
Male gender	12 (63%)	18 (95%)	17 (90%)	47 (82%)
Mean age (+/-SD)	64.4 (+/-8.1)	55.6 (+/-8.24)	62.2 (+/-10.9)	60.6 (+/-10)
Elective	16 (84%)	17 (90%)	18 (95%)	51 (90%)
Diabetes	7 (37%)	6 (32%)	2 (11%)	15 (26%)
Hypertension	8 (42%)	9 (47%)	8 (42%)	25 (44%)
Family History	13 (68%)	11 (58%)	10 (53%)	34 (60%)
Current smoker	5 (26%)	13 (68%)	8 (42%)	26 (46%)
LV dysfunction	3 (16%)	3 (16%)	2(11%)	8 (14%)
Previous MI	13 (68%)	17 (90%)	12 (63%)	42 (74%)

Table 1. Baseline demographics

	Group (1)	Group (2)	Group (3)	Overall
LMS	1	0	0	1
LAD	9	10	15	34
RCA	5	2	3	10
Cx	3	6	1	10
Diagonal	1	0	0	1
SVG to Diagonal	0	1	0	1

Table 2. Lesion subsets (LMS: Left main coronary artery, LAD: Left anterior descending artery, RCA: Right coronary artery, Cx: Circumflex artery, SVG: Saphenous vein graft)

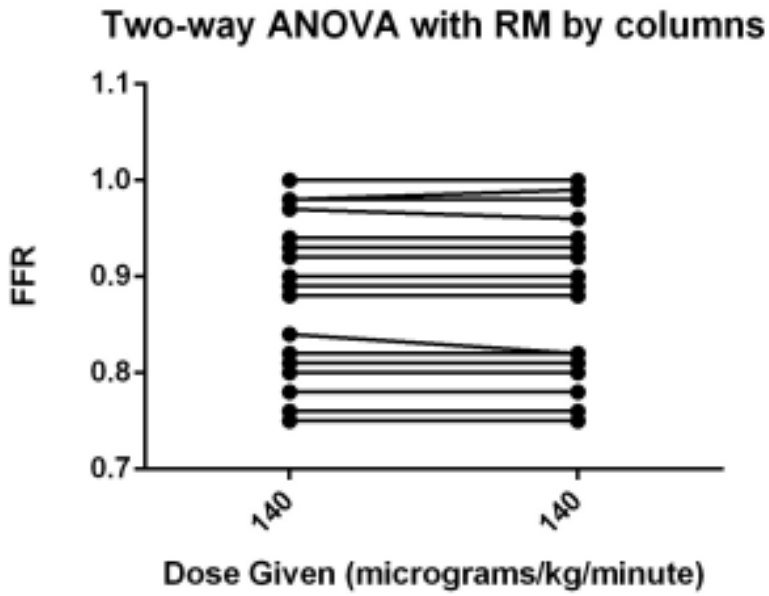
	Baseline FFR	Min FFR dose 1	Min FFR dose 2	P value
Group (1)	0.95	0.88 (0.8-1.00)	0.88 (0.75-1.00)	NS
Group (2)	0.94	0.84 (0.7-0.96)	0.84 (0.68-0.96)	NS
Group (3)	0.92	0.81 (0.7-0.97)	0.79 (0.69-0.89)	NS

Table 3: Fractional Flow Reserve Results

Comparing mean FFR between groups is not useful clinically. Our aim was to determine whether giving a higher dose of adenosine would result in increased detection of haemodynamically significant lesions. With this in mind two way ANOVA analysis was carried out.

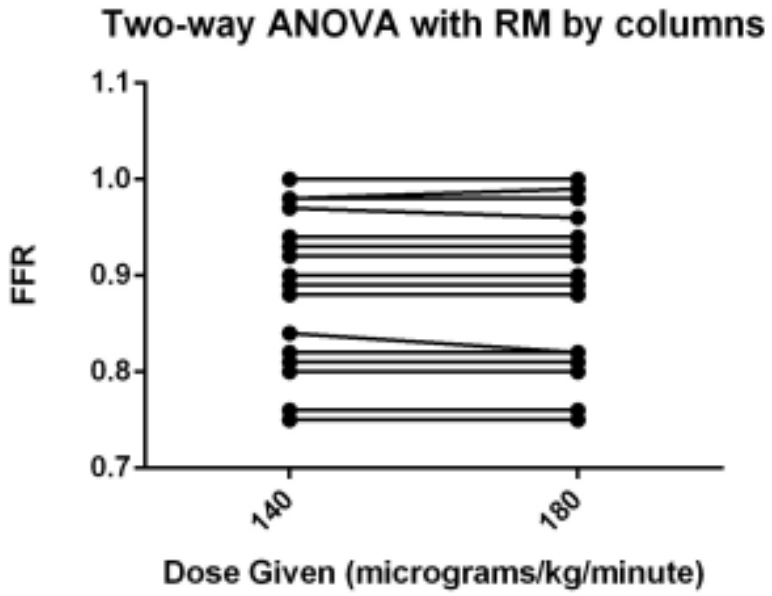
The graphs detail the change in FFR observed with each given dose of adenosine:

(NB an FFR of ≤0.75 is considered to be haemodynamically significant).



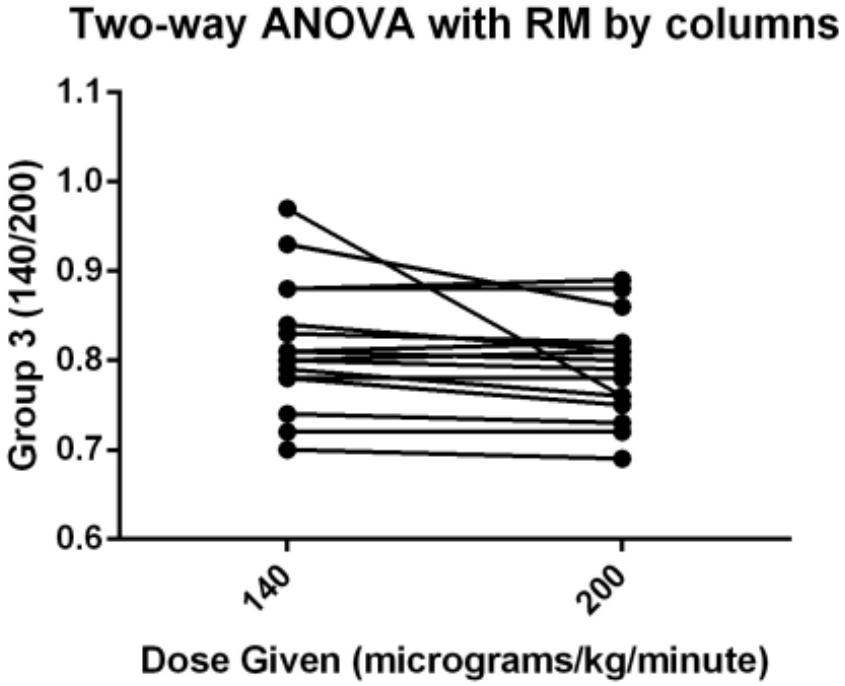
It can be seen from the graph above that no lesion changed from insignificant to significant when 2 consecutive doses of 140micrograms/kg/minute were administered.

The graphical representation of the group receiving 140 followed by 180 micrograms/kg/minute is shown overleaf:



In this group, increasing the infusion rate from 140 to 180 micrograms/kg/minute did not result in any lesion being categorised as haemodynamically significant, which was not so with a dose of 140 micrograms/kg/min.

The data relating to the third group, who received 140 followed by 200 micrograms/kg/min is shown below:



In this group, using the well validated cut off level of 0.8 for a positive study, the FFR value in one patient (5.2%) differed such that the lesion at 140micrograms/kg/min would not be considered significant and at 200 micrograms/kg/min would be significant.

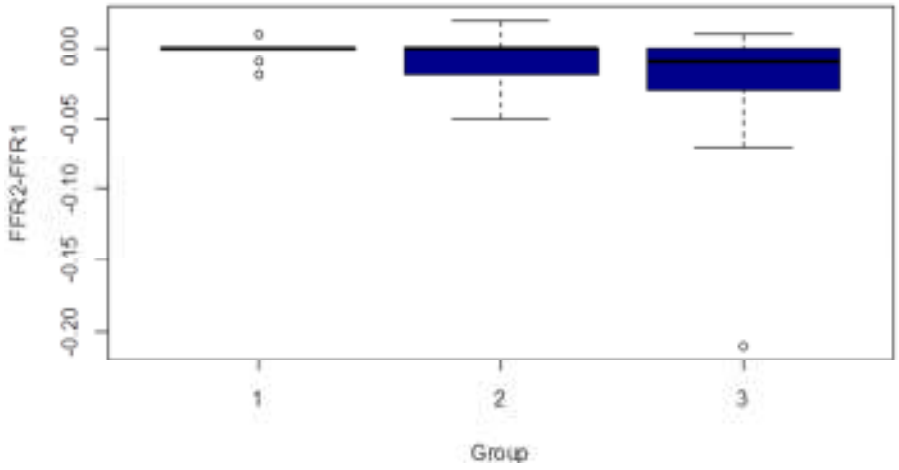
Discussion

Adenosine is the pharmacological agent most often used to induce hyperaemia in the assessment of angiographically intermediate coronary lesions by fractional flow reserve. The fractional flow reserve is a value which reflects the flow down a given coronary artery during maximal hyperaemia, and thus the results are dependent on achieving maximal hyperaemia. The dose of adenosine used currently for this purpose varies widely between operators and institutions, although the major trials (1) used the dose of 140micrograms/kg/min. We set out in this dose-response study to determine whether increasing the dose of adenosine above that used in the major trials (140 micrograms/kg/minute) would result in a significant reduction in the fractional flow level observed.

Conclusion

We investigated the effect of increasing the dose of adenosine in 57 patients attending for coronary angiography either in the elective setting or >48 hours after presentation with acute coronary syndrome. Nineteen patients in each group were randomised to receive 140 micrograms/kg/min followed by either 140 (group 1), 180 (group 2) or 200 (group 3) micrograms/kg/min of adenosine. Each patient therefore served as their own control.

To determine the effect of increasing the dose of adenosine we compared the minimum FFR level measured during a two minute infusion of adenosine at 140 and either 140, 180 or 200 micrograms/kg/min – the effect was recorded as the second FFR recording minus the FFR achieved after the control dose (140micrograms/kg/min), i.e. FFR2-FFR1. The effect of this is demonstrated in the figure below. One patient did not receive the second infusion of adenosine after experiencing complete heart block with the initial dose.



It is noted that there was one significant outlier in group 3 of the data above. This appearance would be consistent with failed administration of the initial infusion. For this reason, the patient was excluded from further analysis.

Using a one way ANOVA to compare the differences, the p value comparing the FFR after 140 micrograms/kg/min to the second dose was, in groups 1-3 respectively: p=0.15, p=0.11, p=0.078. This indicates that although there was a trend to a lower FFR after 200 micrograms/kg/min, this difference was not statistically significant.

In summary, this data has demonstrated that administration of adenosine at doses of 180 and 200 micrograms/kg/min does not result in excess hazard in comparison to the standard dose of 140micrograms/kg/min. The data suggests that although there was a trend towards a reduction in fractional flow reserve with the highest dose of adenosine used that there was no significant difference between the groups.

Suggestion for further study

Further analyses suggested by this study are the effect of varying the dose according to the route of administration (peripheral venous versus administration via a central vein), which could have potentially affected the amount of adenosine which was centrally available. This was not analysed as part of this trial and we left the route of administration to be at the operator's discretion, in order to replicate everyday clinical practice. Differing routes of administration could potentially result in significant variation in the observed fractional flow reserve.

There are currently clinical trials into the utility of using the baseline measurements using pressure wire technology (the so-called wave free ratio), which so far are suggesting that adenosine may be required in only a small proportion of cases undergoing pressure wire study. The data from these trials is awaited with interest. If this method of analysis is widely adopted, there will still be patients who require adenosine to clarify the ischaemic potential of lesions and therefore this data will still be useful.

References

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(4)Pijls NH, van Gelder B, Van der Voort P, et al. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. Circulation 1995; 92:3183–93